RADIATION,
GENES,
AND MAN

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Preface

An event that may prove to have been a turning point of world history took place on December 2, 1942, on a squash court under the stadium of the University of Chicago On that day, unreported because of wartime secrecy, there was started the first man made self sustaining nuclear chain reaction, for the first time men obtained energy from a source not derived from the fires of the sun Science has thus forced man to enter a domain from which there is no turning back and no escape Only two roads lie open One leads to material advance, universal brotherhood, and spiritual fulfillment The other leads to disaster and possibly to extinction The use of atomic energy opens before mankind vistas of unheard-of power, its misuse endangers the most precious possession man has or can have—his innermost nature Such misuse threatens genetic damage to generations yet unborn, it is a menace to our posterity, both close and remote.

This book is about the threat of genetic damage to man—a topic which has been discussed frequently in books, in journal articles, and in the daily press But the appearance of yet another book dealing with it hardly needs justification The subject will doubtless remain in vogue for a long time, since man cannot afford to be indifferent to his future As we improve our understanding of the situation created by widespread and ever-increasing use of high energy radiation and atomic power, it will become necessary from time to time to restate and revise the conclusions concerning the dangers of genetic damage

We have endeavored to make this book understandable to

the general reader, not to biologists alone But we resolved not to impose upon the reader our own opinions and conclusions without giving him at the same time some competence to judge their validity for himself A number of scientists, including very eminent ones have made pronouncements, some declaring that the genetic damage from radiation places mankind on the brink of disaster, others contending that the damage, if any, will be slight or negligible We felt that merely adding declarations of our views to this not very edifying multiplicity of beliefs would be less than useful Probably the most important fact concerning the issue is that the data evidence, and information on which, and only on which, conclusions should rest are as yet wholly inadequate Partisan statements usually conceal this insufficiency of knowledge to avoid exposing their partisan nature We intend, on the contrary, to stress the need—indeed, the urgency—of further research on the genetics of populations and on radiation genetics

An evaluation of the magnitude of genetic radiation damage to human populations can be at best very tentative at present To appraise such evaluations, the reader must be able to see the strengths and weaknesses of the arguments on which they rest This has necessitated the discussion of some topics that will perhaps be regarded as abstruse, particularly in Chapters 6 through 8 If, despite our efforts to alleviate the difficulties, the reader is terrified by these chapters, he can be advised merely to skip the difficult places We hope that the conclusions are stated understandably, but we prefer not to have them accepted on faith by those who are able to assess their validity We do not claim for these conclusions more than that they seem reasonable to us on the basis of the information now available New discoveries, new information, may well change them Science is often most convincing when it is least dogmatic

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Atomic Energy— Friend or Foe?

Prometheus, Old and New

According to Greek myth Prometheus stole fire from heaven, brought it to earth, and gave it to men to make them happy and powerful and proud For this act of defiance, he was doomed by Zeus to endless suffering Although nowadays people are disinclined to invent myths of the kind the ancient Greeks created so well, the release of atomic energy was a feat of almost Promethean daring To all but a handful of physicists, the release of energy through the fission and fusion of atomic nuclei seems like magic If we had not seen photographs of atomic explosions and of the havoc wrought by them we might disbelieve the whole notion of atomic energy Even with all this evidence before us, the fact that the amount of energy released in these explosions can be calculated only with the aid of a formula which involves multiplying the speed of light by itself defies ordinary comprehension

There is no way of telling just when and how fire was first tamed by man The real Prometheus is lost in the mists of

prehistory We know only that remains of charcoal from the hearths built by Peking Man are found in abundance, together with his bones, in the cave shelters not far from Peking, China. Peking Man is one of the links connecting biologically modern man with his apelike ancestors, his remains are perhaps as much as half a million years old The use of fire was doubtless one of the great achievements in the long and slow ascent of our remote forebears from an animal to a true human level Fire permitted our ancestors who were originally inhabitants of warm countries, to invade lands that were otherwise too cold for them in winter, and eventually to spread to all continents and most islands all over the world Fire rendered possible the cooking of food, and thus increased immensely the range of foodstuffs with which man could satiate his hunger Much more recently, some 4,000–5,000 years ago, fire was used to extract metals from ores and to work them into tools which gave man his dominion over his environment Especially from the time of the Industrial Revolution, fire has been the basis of many of man's laborsaving devices

The history of man's mastery over fire is, however, a history of both good and evil Many a house, village, and city, with all its inhabitants, has been given to fire and sword Only few centuries ago, thousands and thousands of people, whose crimes were chiefly those of conscience, were burned at the stake Today we have fire extinguishers in many buildings and maintain town fire brigades Folk wisdom warns that it is inadvisable "to play with fire Yet it occurs to nobody to suggest that we ought to give up the use of fire, we simply minimize fire hazards *Man has learned to live with fire He will have to learn to live with atomic energy*

The story of atomic energy is in some ways like the story of fire, although the atomic Prometheus was our contemporary This new Prometheus was not a single person but a group of brilliant physicists and mathematicians, who toiled for many years, and in different countries, to uncover secrets of nature, unmindful of any possible practical value of their findings Many of them, in fact, belonged definitely to the class of impractical dreamers commonly known as eggheads, and they were

so regarded even by some of their more hardheaded, or real istic, colleagues One of the authors of this book remembers a discussion, around 1940, with a very able but very ' realistic physicist, who gave the work of Einstein and Bohr as an exam ple of a kind of science that would never benefit humanity Little did he know that perhaps at that very moment, Franklin D Roosevelt was authorizing considerable expenditures to make possible scientific research recommended by Einstein and others A few years later, under the leadership of Enrico Fermi among others, this research led to the release of atomic energy in the first atomic pile The scene of this event was a squash court of the University of Chicago

None of the scientists who worked to bring about the release of atomic energy was chained to a cliff, like the Titan Prometheus But perhaps the consciences of some were lacerated by the dreadful use awaiting their glorious discoveries For the first willful employment of atomic energy was in the atomic bombs which killed and maimed perhaps more people in Hiroshima and Nagasaki than were ever burned at the stake by the Holy Inquisition

Do We Need Atomic Energy?

There is a popular belief, which may or may not be true, that monkeys can be trapped through the use of a small mouthed jug containing several rather large nuts The monkey, so the tale goes, finds the nuts in the jug and reaches his paw in to take one Grasping the nut the monkey s paw is too large to be withdrawn from the jug Escape could be accom plished simply by releasing the nut and walking away But the monkey refuses to let go, he is trapped

Much as we may hope that letting go' offers one possible solution to the problems raised by the Atomic Age, it is highly unlikely that we will escape any more successfully than our simian friend The atom is too tempting, we will refuse to let go The reason the atom is here to stay—in spite of its many

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able in a great many areas of the earth and that, even in the United States it is sufficient to supply only a fraction of the total energy we now consume

This point can stand further amplification In an ordinary home, it is common for several lights to burn throughout an evening, six 100 watt bulbs burning for three hours is not unusual The energy required to keep these bulbs lit for this period of time is equivalent to nearly 5,000 000 foot pounds, that is, to the energy that would be embodied in a Cadillac hitting Thirty fourth Street if it were thrown from the top of the Empire State Building The Niagara Falls are 160 feet high, about 15 tons of water must pour over the falls in order to supply the energy required for lighting this one house This assumes that hydroelectric plants are 100 percent efficient, if their real efficiency is nearer 10 percent, 150 tons of water are required This does not seem to be a particularly great amount of water (at the usual rate of flow for the Niagara River, it would require about 0 0025 seconds for this much water to flow over the brink) until one starts counting the number of homes with electric lights Add to this the number of TV sets watched during the same evening Include various household appliances, power tools, and oil burners And finally, include industrial processes such as the extraction of aluminum, which demand large quantities of electricity

Rather than add all of these individual demands, it is simpler to proceed from the other end The total production of electricity in the United States in 1955 was approximately 600 000,000,000 kilowatt hours We saw that 1 8 kilowatt hours (600 watts $\times$ 3 hours) was equivalent to 5,000,000 foot pounds The total consumption of electricity per year, then, is equivalent to $1\ 5 \times 10^{18}$ (1,500 000 000,000 000,000) foot pounds With a mean height of 160 feet, a flow of 200,000 cubic feet per second, and a 10 percent efficiency of hydroelectric plants, it would require about 250 Niagara Falls to satisfy this demand In fact, if every drop of water that falls on the United States as rain were collected and were forced to run to the sea by way of a hydroelectric plant, it is doubtful whether our present demand for energy could be satisfied in this way

What, then, are our sources of energy other than water

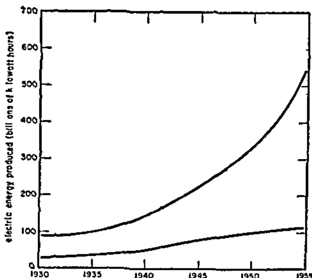


FIGURE 1 Annual production of electric energy in the United States between 1930 and 1955 Upper curve—total energy produced lower curve—energy produced by hydroelectric stations

power? About 80 percent of our total electrical output comes from burning coal, gas and oil Figure 1 shows that the demand for electricity has climbed at an ever increasing rate for the past 25 years today we consume about six times as much as we did in 1930 During the thirties water power was a substantial contributor to the total amount of electricity consumed At present it is only a minor contributor, moreover, the amount of electricity produced in this way has become nearly constant As the demand grows then water will become even less important in the over all picture By fulfilling an ever increasing demand for power by burning fossil fuels—coal, gas and oil—we are depleting stores which are not being replaced These are non renewable natural resources and we have not been overly prudent in their expenditure Despite claims that there are oil and gas fields as yet undiscovered and coal fields still unworked whatever quantity exists is fixed In time—and in an alarmingly short time if the demand grows as it has for the past quarter of a century—these fuels will be gone

There are two energy sources that may replace fossil fuels

as the supplies of the latter approach depletion One is radiation from the sun, the other is nuclear energy—that derived from the fission of heavy atoms and the fusion of light ones It may be noted that all energy which man has used so far is derived ultimately from the life giving warmth of the sun Plants capture solar energy by means of their green pigment, chlorophyll, and store it in energy rich chemical substances The existence of all other organisms—men, animals, and plants without chlorophyll—is entirely dependent upon their being able to utilize these substances as foods, and thereby to utilize at second hand, as it were, some of the solar energy captured by chlorophyll The energy obtained by burning wood is again that of the sun stored by a green plant, the fossil fuels represent accumulations of solar energy stored by plants of ages long gone by And finally, the energy of running water and of wind is derived from the warmth of the sun rays, which causes the evaporation of water from the surface of the sea and the circulation of air masses The tremendous historical significance of the release of atomic energy is that man has, for the first time, learned how to obtain energy from a source that is not merely transformed solar energy.

It might seem that capturing solar energy directly would be preferable to utilizing atomic energy, with all the dangers inherent in the latter However, the practical utilization of solar energy at present is restricted to rather small solar batteries It is possible that these will eventually be developed into a substantial source of energy At the moment, though, atomic energy is far in the lead We know that enormous amounts of energy can be released by fission and fusion processes We know how to exploit the energy of fission In the case of fusion, we have yet to learn how to control its release, but this will probably be accomplished in the not too distant future Man will certainly not release his grip on this source of energy.

The Dangers of Atomic Energy

If playing with fire is dangerous, playing with atomic energy is far more so Animals, at least those living on land in

tropical and temperate climates, often encounter rocks and soil heated to excessively high temperatures by the summer sun Living beings possess sense organs that detect such excessive heat in the environment and stimulate them to move away to cooler places Atomic radiations of considerable intensity, however, do not occur naturally on earth, they are man made Our bodies, and those of other organisms, have no sense organs that detect exposure to such radiations and warn us by giving a danger signal Yet these short wave radiations (see Chapter 4) produce, in a matter of days or weeks after exposure, burns just as dangerous as those produced by excessive heat Still more insidious is the power of these radiations to evoke malignant growths, or cancers These malignancies may not appear for years after exposure

However dangerous radiation burns and radiation induced malignancies may be, these maladies affect only persons directly exposed to radiation Ailments caused by radiation in exposed persons are referred to collectively as "physiological radiation damage" One may derive some comfort from the fact that physiological damage is at least confined to the generation irradiated More ominous is the genetic damage induced by radiation The sex cells of a person exposed to atomic radiations may be altered so as to produce death, disease, monstrosity, invalidism, or simply delicate health in the descendants of irradiated individuals This morbid alteration of the hereditary materials may menace any number of persons, because it may be transmitted generation after generation for a long time to come A great many persons believe that genetic radiation damage may endanger the future of mankind

The seriousness with which physiological and genetic dangers are regarded can be judged from the actions taken by many governmental and quasi governmental agencies The United Nations Scientific Committee on the Effects of Atomic Radiation is attempting to gauge, from existing data, the dangers of irradiation and to indicate the lines of research that may make more accurate judgments possible in the future The World Health Organization convened a committee of geneticists in Copenhagen during the summer of 1956 to consider similar problems

In the United States we have had hearings conducted by the Special Subcommittee on Radiation of the Joint Congressional Committee on Atomic Energy the subject of these hearings at which many scientists testified was the nature of radioactive fallout and its effect on man The National Academy of Sciences has made a study of the biological effects of atomic radiation The governments and scientists of many other countries—Great Britain India and Japan for example—have delved into these same problems

Scientific and Ethical Aspects of Genetic Radiation Hazards

Perhaps no other scientific discovery has had the emotional impact that the release of atomic energy has had But the pride elicited by this brilliant attainment of the human spirit is mixed with fear The destructiveness of atomic explosions and the hazards of radiation have aroused the fear that if not our own generation then our descendants will find the Atomic Age an impossible one to live in And if man does survive there is the appalling possibility that human nature itself will be deformed and wrecked by misuse of this terrible new power

The public even the so-called educated public gathers its information about atomic energy and the dangers of radiation chiefly from the daily press and from articles in popular magazines Unfortunately newspaper and magazine reports have all too often dealt with bogus sensations—impending extinction of mankind through sterilization or through wholesale production of inhuman monsters On the other hand efforts more often glib than well grounded have been made to minimize the very real hazards of radiation

How can the public arrive at a reasonable attitude toward both the need for and the dangers inherent in the use of atomic energy? One possibility of course is that the matter is altogether beyond human reason Faced with a seemingly incomprehensible situation one can forsake reason entirely and rely solely on instinct or intuition We are not this pessimistic We

believe that the situation calls for an understanding of the problems involved Under pressure of public opinion, a variety of official decisions regarding possible courses of action will be taken If these are to be intelligent decisions, if they are to stand in the face of opposition arising out of selfishness or ignorance, it is imperative that the public comprehend the issues at stake

The purpose of this book is to spell out, to the best of our ability, the genetic aspects of the problem of atomic—and other—radiations We do not believe, however, that all the answers to the problems created by atomic energy are to be found in genetic or any other scientific information Some of these problems involve ethical rather than factual considerations Consider, for example, a statement not unlike some that have repeatedly appeared in the press Fallout causes leukemia, bone cancer, and endangers future generations, therefore, bomb tests must be stopped Although the premise is certainly not irrelevant to the conclusion, it is not in itself sufficient to make the conclusion necessary It is possible that the testing of bombs should be stopped immediately even if fallout were harmless on the other hand, it may be that these tests must be continued regardless of their dangers even though these be a hundred or a thousandfold greater than we think they are

There are people who hold that scientists should not leave their laboratories and attempt to write a book of this kind But scientists and nonscientists must share equally, man for man, the responsibility for the ultimate decisions regarding the use of atomic energy It is wrong to restrict either responsibility or privilege in these matters We reject the view that only those with access to secret information are qualified to hold opinions about these issues, "secret information is used here both with reference to classified information and with reference to information that is not generally known

If decisions based on rational thinking are preferable to those based on intuition, then anyone who has relevant information or an opinion based on such information ought to share this knowledge with others. Sharing information does not guarantee unanimity of final judgment, it does, however, offer each

person an opportunity to identify that point at which his views diverge from those of his neighbor A scientist for example who finds that his technical information is accepted but his recommendations on policy are not is entitled to know why not he then has an opportunity to re examine his own reasoning Every individual is entitled to information pertinent to a given decision If one finds it impossible to agree with conclusions reached by others he is entitled—more than that obligated —to inquire whether pertinent information has been denied him He is obligated to inquire and if necessary to demand that this information be placed at his disposal

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Heredity, Environment, Genes, and Chromosomes

Man and Biology

An understanding of the genetic problems raised by irradiation requires some knowledge of biology, particularly of genetics, which is the science of heredity, and also of physics, particularly of radiation physics In this and in the following two chapters we shall attempt to give a simple account of the fundamental and relevant facts of genetics and of radiation physics which will be needed as a background for the discussion to follow.

Quite often this discussion will focus on experiments carried out with organisms other than man—*Drosophila* (the 'vinegar' or 'fruit" fly), mice, and even bacteria This may seem strange to some people, who will contend that problems pertaining to human beings must be solved by studies on human beings Others may say that organisms such as monkeys or, at the very least, mice can throw some light on man, but that vinegar flies and plants and bacteria are too much unlike man to tell us anything worth while.

We do not for a moment believe that man is nothing but an animal In man biological evolution has transcended itself Man is not an overgrown fruit fly, or an overgrown mouse, or merely an especially clever monkey Man alone is the creator and possessor of culture, he alone can think in abstract symbols and use symbolic language Organisms other than man become adapted to their living conditions, to their environment, chiefly by changing their biological nature through the relatively slow process of evolution Man alone can adapt himself by changing his environment as well All organisms, including man transmit their biological heredity to their offspring by means of materials contained in their sex cells Man alone can transmit his thoughts his inventions, and his skills by means of instruction and learning, to other human beings who are neither his children nor even his contemporaries Clearly, we must avoid both types of error—that of treating man as though he were nothing but an animal and that of forgetting that human nature does have a biological basis It is this biological basis which may be en dangered by radiation exposure

Biological sciences progress by building intellectual out posts far beyond the frontiers of general knowledge These bold advances are made as the result of new techniques and new ideas, they are based generally on the study of the most diverse organisms The outposts then establish connections and out of the union of distinct types of studies further spectacular ad vances are made Meanwhile many gaps are left in our knowl edge These are slowly filled by studies of more and more types of plants or animals Long before the gaps are filled, however, missing information can be predicted with remarkable accuracy from established points of cross reference Who for instance, has ever seen a hummingbird killed by lightning? But who doubts that lightning can kill a hummingbird? In the case of genetic studies, man has served primarily, though not exclu sively, as material with which to confirm and to which to apply the discoveries made with other organisms And so, despite the fact that we are concerned with the effects of radiation on man, our factual knowledge of the types of damage and the relation between damage and exposure will come largely from common

experimental organisms such as bacteria yeasts molds fruit flies and mice

Individual Variation

It is a matter of general knowledge that no two persons are ever exactly alike Even so-called identical twins are never really identical although they may be more strikingly similar than persons who are not twins Identical twins result from the division of a single fertilized egg cell into two or more separate fetuses which eventually become separate infants and separate adults Such twins inherit precisely the same genes from their parents They are identical in their heredity Other twins (called fraternal) result from different maternal eggs fertilized by different paternal spermatozoa They are really brothers or sisters born simultaneously they differ in their heredities and they are often quite dissimilar in appearance although no more so than brothers and sisters who are not twins

What is the source of the differences between individuals? This is a very general biological problem for just as there are no two absolutely identical persons so there are probably no two identical individuals of any biological species Part of this variation we recognize as environmental and part we know is inherited It is common knowledge that the weight of an individual is related to the amount and type of food he eats Undernourished persons lose weight and become emaciated It is however not rare to find that of a number of persons with essentially the same diet some are stout while others are thin (see Figure 2) In the case of skin color we know that some persons remain dark even when not exposed to sunlight On the other hand we know of other persons who do not tan upon exposure but burn or freckle instead Sometimes we are acquainted with the parents or grandparents of these same persons and we are familiar with the fact that similarities may run in families for many generations

HEREDITY
ENVIRONMENT
(DIET)
STARVATION
AVERAGE
COPIOUS
THIN
GENOTYPE
FAT
GENOTYPE

FIGURE 2 Interact on of heredity (genotype) and environment Persons who inherit from their parents genotypes wh ch predispose them to being skinny or thin lose or gain weight depending upon their diets So do persons who inherit a predisposition to be corpulent fat or obese However if the diets are very different some people with thin genotypes may actually weigh more than persons with fat genotypes

Some family traits are passed on from one generation to the next in a much clearer fashion than others Eye color hair color blood types pattern baldness and certain abnormalities of the fingers and toes are affected only slightly by the conditions under which a person is raised by examining family albums one can discern the occurrence of some of these traits through a number of generations Other traits such as height weight intelligence and personality characteristics are profoundly in fluenced by such factors as diet education and the environ mental tenor of the home It is frequently difficult to decide

whether heredity has played any role at all in the determination of these traits

Nature and Nurture

Labile traits—those which are easily influenced by the environment—often comprise the most important or the most interesting aspects of an individual's personality in his relation to other persons This fact brought about the 'nature versus nurture' controversy, which was particularly lively several decades ago The debate centered on the relative importance of environment (nurture) and heredity (nature) in the development of a human person As a matter of fact, the controversy still reappears every now and then, although to a large extent the debates have been rendered meaningless by modern genetics

Every person is born with a certain genetic endowment inherited by him in the egg and the sperm from which he arose This endowment enables the individual to survive under a certain range of environmental conditions What, then determines the path which the development of a person will take? The genetic endowment, the individual's *genotype*, interacts with the particular environments—intrauterine, individual, family, group, class, regional, and national—in which the person lives his particular life These interactions determine the characteristics by which we know the person, his *phenotype*

In a limited sense we can think of the genotype as establishing certain potential capacities, which are then realized with greater or lesser success under various sets of environmental conditions Thus, certain congenital idiots by virtue of their genotypes, are incapable of learning even the simplest things, no amount of teaching will result in normal mental development On the other hand, persons capable of learning a great deal may not have an opportunity to develop their potentialities Since the potentialities of any one individual form a complex pattern, it is doubtful whether any environment suffices to

develop every facet of an individual to its utmost In certain instances the development of different facets is undoubtedly mutually exclusive At some stage in life a person of many potential talents must choose the few on which he will concentrate his efforts the others will suffer by his choice

Some hereditary traits, however, seem to be unaffected by the environment The best examples of such traits may be found among the properties of the blood, or, more precisely, of the red blood cells These properties have much to do with the safety, or danger, of blood transfusions If two persons belong *to the same blood type, the transfusion is safe if to different* blood types, the transfusion may or may not be dangerous Blood types are inherited according to simple Mendelian rules of which we will say more below The aspect of the matter which interests us here is that the blood type of a person becomes recognizable even before birth, persists throughout his entire life, regardless of his state of nutrition and health, and can be diagnosed even in his bones many years after death Such traits which are apparently independent of the environment are in reality traits which develop in all, or at least in all known, environments in which life is possible

In any case, it is impossible to draw a sharp distinction between hereditary traits and environmentally conditioned traits The nature nurture controversy is thus reduced to the relative importance of heredity and environment in the development of this or that trait Relative importance, in turn, becomes a function of the distribution of environmental and hereditary factors in space and time Malaria may be absent in some areas because the malarial parasite or its carrier mosquito is absent, in other areas where malaria is prevalent, resistance or nonresistance may be conditioned by heredity, as it is in some areas of Africa In the northeastern United States tan skins are a function of the season, in the Southwest, tanning may be the normal state of affairs individuals who are unable to develop skin pigmentation in that region are unable to do so because of their particular genotype For personality characteristics, one need not pass from one geographical region to another in order to illustrate the alterations in the relative im

portance of environment and heredity one need only go from home to home

An understanding of the interactions between the environ ment and a person s genotype does much to abolish the resig nation which used to accompany the discovery that a given condition or disease was hereditary Frivolous examples of how ladies are able to defy their heredity can be derived from the role of beauty parlors in producing desirable women Such examples are not entirely irrelevant for in a sense medical advances in the treatment of hereditary diseases are based on the same principle modification of the environment so that a given genotype will produce a normal healthy individual in stead of the expected infirm or crippled one Thus although no amount of training can at present improve the mental status of certain congenital idiots it is not beyond the realm of possi bility that man may some day discover how to correct the physi ological defect which is responsible for this hereditary trait

Heredity Is Not a Status but a Process

We have spoken above of the inheritance of traits —eye or skin color blood types and hereditary diseases—as though each trait were inherited separately and independently of all others This manner of speaking is convenient because it is rooted in everyday language one hears of a child having in herited his eyes from his mother the shape of his face from his father and his freckles from one of his grandparents But it can be seriously misleading if taken literally Heredity is not a gradual addition of unit traits or characters the sum of which makes up the person or the individual We do not really inherit eyes noses freckles or diseases what we do inherit are genes contained in the sex cells whose union starts the develop ment of a new person

This matter is understood most easily if approached not from the end product the adult organism but from the or

ganism's beginning, the newly fertilized egg The fertilized egg in which every human starts his existence, is a tiny speck of jellylike material barely visible to the naked eye But this very special jelly grows and develops into an embryo, a fetus, an infant, a youngster, an adolescent, an adult, an oldster, and, finally, a cadaver It grows and exists because it consumes food which it takes in from its environment—at first from the body of its mother, and then in the form of regular meals It trans forms its food into the constituents of a living body, into itself *There is, however, nothing haphazard about this transforma* tion, the development of a body proceeds along a definite path, from an upswing of vitality in childhood and youth to decline and final dissolution in old age

What heredity really does is to define the path taken by the development of a particular individual in the particular sequence of environments encountered by this individual dur ing his lifetime The path is unique for each individual human being, but at the same time, it is related to that of his parents and ancestors It is unique because, as we shall see below every *person inherits a constellation of genes which is different from* that of every other person and because no two persons have exactly the same sequence of life experiences It is related be- cause the genes which comprise the hereditary constellation of each individual are derived from ancestors close and remote back to the beginning of life on this earth

When we speak of a person and try to describe this person to others, we can do so most easily by specifying separately the traits and characters which we observe This isolation of traits and characters is then, a necessity, or at least a convenience, imposed by the structure of the language we speak or write Let us not, however, be misled by this language into thinking that heredity is equivalent to fate Since the developmental path *of every person is determined by his heredity and by his en* vironment, it can in principle be modified by either *If a given* genotype yields an undesirable trait, such as a hereditary disease, in one environment, it may yield a different, healthy trait in a different environment The problem is what environment, or rather what sequence of environments, the genotype of each

particular person needs to produce the best result, the best phenotype

Public health and educational authorities endeavor to devise environments in which most human genotypes—loosely referred to as normal —yield reasonably satisfactory persons, workers, and citizens Those genotypes which do not do so well in these environments result in people who are abnormal, deviant, or diseased Some of these unfortunates could, however, do better in environments better suited to them Finding out how to create such special environments is the task of medical science, which has already made great strides in this direction Medicine is not yet able to engineer good environments for certain human heredities, so these continue to produce incurable diseases Some of these conditions will certainly be alleviated in time

Chromosomes and Nucleic Acids

The formation of a new individual begins when a sperm unites with an egg Sperm and eggs are the sex cells, or *gametes* produced by the individual s father and mother respectively The genetic endowment—the genotype—of the person is contained in the two uniting sex cells

Fertilization, the union of an egg and a sperm brings about two important events First, there is a union of genetic material The egg and the sperm each contain, in man 23 *chromosomes*—small bodies which, in microscopic preparations stain with certain dyes A fertilized egg cell comes, then, to contain 23 *pairs* of chromosomes 46 in all, one member of each pair derived from the mother and the other from the father Second, a fertilized egg cell divides, and redivides again and again, until, from an initial glob of jellylike material smaller in size than a period ( ), a human being is formed At every division of the egg cell and of the cells that are derived from it, every chromosome is duplicated, one of the resulting new chromosomes passes to each daughter cell Therefore, most cells of the body contain

46 chromosomes Furthermore every cell contains a chromosome descended from each of the 23 maternal and 23 paternal chromosomes that were combined at fertilization We are children of our parents in every one of the many billions of cells that compose our body

The two parents mother and father contribute equally to the heredity of the child Yet the male and female sex cells are about as unlike as cells can be An egg cell has a mass thousands of times that of a sperm while the sperm has a tail by means of which it can swim about the egg is immobile its cytoplasm being laden with nutrient materials for the new organism The chromosomes are the only constituents which are alike in the female and male sex cells It was this similarity of the egg and sperm chromosomes which led some nineteenth-century biologists to infer that chromosomes are the physical carriers of heredity This inference has since been amply confirmed in many ways

In recent years some insight has been gained into the chemical composition and structure of the chromosomes for the first time consequently we have an inkling of how they function as carriers of heredity Apparently the most important constituent of the chromosome is an extraordinary chemical substance known as DNA (desoxyribonucleic acid) The molecules of this substance are long stringlike fibers Because they are bundled into chromosomes these fibers can be apportioned in an orderly way at each cell division, in the absence of such packaging the cell nucleus would resemble a thread factory operated without spools DNA molecules are frequently compared to the tapes which control modern business machines because it is almost certain that the physical structure of DNA fibers does indeed carry the code for all of the vital functions performed within living growing and dividing cells

The incredible efficiency of the DNA coded tape can be illustrated by saying that all of the chromosomes present initially in the fertilized eggs from which the present population of the world (some two and a half billion people) developed would occupy a volume about equal to that of an ordinary aspirin tablet In addition DNA has a further property not shared by

any man made tape Its structure is such that by attracting to itself the relatively simple chemical substances of which it is composed and which are present within cells, it can make a complementary copy of itself Because of its chemical structure and the spatial relations between the constituent molecular parts it is capable of self duplication, correct in every detail

Of what use is a complementary copy, a mirror image of the molecule? The answer to this question reveals another remarkable property of the DNA molecule As shown recently by J D Watson and F H C Crick, the structure of DNA consists of two chains which are complementary copies of one another Separate these chains let each build a mirror image, and you have two molecules of DNA where you originally had one And the two new molecules are precisely the same in structure!

Self duplication is, of course, the basis of life We see it on a grand scale by watching the multiplication of living things But self reproduction must happen within organisms, on a molecular level, as well We said that the newly fertilized egg divides over and over again At each division both daughter cells get a full complement of 46 chromosomes, but the repeated division of these chromosomes does not mean that the chromosomes get smaller and smaller The process of 'division,' or *mitosis*, is actually one of duplication or replication With the possible exception of the first few divisions of the egg, development involves growth—the manufacture of proteins and enzymes, and the construction of new molecules of DNA

Each of the 46 human chromosomes attracts to itself the material necessary to make an exact duplicate of itself, a duplicate whose precise similarity to the original is guaranteed by the chemical structure of the DNA molecule Only then does the cell divide each of the 46 chromosomes going to one of the new cells while its newly constructed duplicate goes to the other Hence, each cell in the body, with the exception of a few expendable kinds such as red blood cells, has its full quota of chromosomal material copied very precisely from the original models carried by the uniting egg and sperm

Meiosis

We might ask what happens when an adult individual—man or woman—produces sex cells of his own We have seen that, unlike the cells of the body, each sex cell contains 23 chromosomes rather than 23 chromosome *pairs* Obviously, the number of chromosomes must somehow be reduced by half

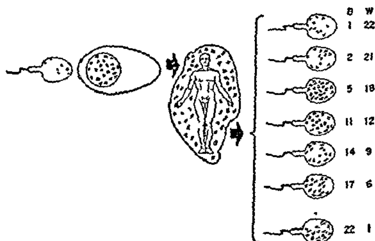


FIGURE 5 Sex cells produced by a person may carry different combinations of his chromosomes A spermatozoon with 23 chromosomes shown in black and an egg cell with 23 chromosomes *shown in white are represented schematically on the left.* Union of these sex cells yields a zygote a person whose body cells contain 46 chromosomes (shown in the middle) The sex cells of this person will again carry 23 chromosomes but, as shown on the *right different sex cells will have different numbers* of black (B) and of white (W) chromosomes.

This reduction occurs in two special divisions of the cells contained within the reproductive organs, or *gonads—testes* in the case of males, *ovaries* in the case of females These special divisions are called *meiotic divisions* or, simply, *meiosis* During these two divisions the chromosomes build replicas of themselves only once The two members of each pair, each member with its newly manufactured copy, approach one another very closely to

form 23 four parted compounds The cell then divides twice The first division separates the two "original' members, each—accompanied by its copy—going to a separate cell This division is followed immediately by a second, which separates each chromosome from its copy Thus, the reduction from 23 pairs of double chromosomes to 23 single chromosomes, one of each of the original pairs, is accomplished

Although this process involves some additional steps, it is sufficient for our present purpose to regard these cells, with their reduced number of chromosomes, as the final sex cells Thus we have seen how two sex cells, each carrying 23 chromosomes unite to give an individual with 23 pairs of chromosomes, and how the individual, with his 23 chromosome pairs, produces sex cells with 23 chromosomes each (Figure 3)

Genes

So far we have discussed the chromosomes as units, and in their maneuvers during cell division they behave as such In a physiological sense, however, a chromosome exerting its control over life processes is a body composed of a great many smaller units These are the *genes* There may be hundreds or thousands of genes in every chromosome Genes are localized regions of the chromosome—probably of the DNA molecule—which control specific physiological or biochemical processes Just how sharply neighboring genes in a chromosome are demarcated from one another, or how distinct they are in a physical sense, is somewhat uncertain In classical genetics, the genes in a chromosome were often compared to a series of beads on a string the string being some sort of skeleton of the chromosome Certainly, this bead on string model oversimplifies the actual situation Perhaps a better way of visualizing the relation between the two is to say that a chromosome is composed of genes just as a motion picture film is composed of different scenes Although the transition from a love scene to a chase to a gun fight may be gradual, still there are these different scenes A given region of a chromosome

is concerned primarily with a given physiological and biochemical process, and in this sense, at least, different regions can be referred to as units, as genes

All the genes contained by the chromosomes act in concert to bring about the development of the organism A given gene seems to function by manufacturing a biochemical substance, such as an enzyme which facilitates certain chemical reactions Biochemical geneticists have found it possible, chiefly in simpler organisms such as bacteria, yeasts, and molds, to associate many genes with the enzymes and the chemical reactions they control If a certain gene functions properly, the physiological process which it controls proceeds normally If, however the gene is destroyed or altered in some way, the bacterial cell which lacks the gene, or carries only its altered form, may be unable to carry out a certain physiological function and may die In some instances bacteria with such a 'hereditary disease' can be "cured' by adding to the nutrient medium on which they grow the chemical substance which the defective gene fails to supply but which normal bacteria are able to manufacture in their own bodies It is by means of this technique that we learn of the nature of chemical reactions vital to life itself

Some hereditary diseases in man have genetic and biochemical bases almost as simple as those of the bacteria mentioned above Thus one of the defective genes in man, when inherited both from the mother and from the father, produces a disease known as *thalassemia* or Mediterranean anemia Individuals carrying this defective gene in double dose show symptoms of a severe anemia and usually die before the age of adolescence L Pauling and H A Itano discovered that the red blood cells (erythrocytes) of the anemics carry, instead of the normal red pigment, hemoglobin, a chemically altered form of the hemoglobin molecule Persons who are heterozygous for thalassemia—that is, who have inherited the defective gene from only one of their parents, enjoy normal health or are only mildly anemic The red blood cells of such persons contain both normal and abnormal hemoglobin It is as though the normal and the abnormal variants (alleles) of this gene facilitated chem

ical reactions yielding the normal and the abnormal hemoglobin respectively

The chemical substances produced by gene controlled re actions are, however, by no means always known Ordinarily, genes are recognized because they occur in two or more forms, which produce alterations of externally visible bodily traits In fruit flies, for instance, the normal functioning of many genes leads to the development of the usual dark red eye color But some of these genes from time to time suffer alterations (referred to in genetics as *mutations*) which produce variant (allelic) forms of the genes Several of these altered genes result in eyes of a very bright red color, instead of the normal dark red Similarly, the malfunctioning of a number of other genes makes the eye color brownish red When a fly carries both the altered genes yielding the bright red and the brownish red eye colors, the combined action of these genes results in an eye color of pale pink or white White eyes are also produced by the mutation of still other genes, which evidently control the production of both the bright red and the brownish red pigments

A great many traits are known to be controlled by genes Even those controlled by the genes located in one chromosome can be of the most varied kinds In Drosophila, for instance, some well known genes (well known to geneticists that is, and of especial importance to their work) located in one particular chromosome control body color, bristle formation eye color, size of the fly, eye shape, texture of the eye surface, leg shape, and wing venation In man a list of traits controlled by genes located in the chromosome that also determines the sex of an individual includes color blindness, several skin abnormalities, and an abnormality of the retina of the eye

Mendel's Law of Gene Segregation

We are already familiar with the fact that human sex cells, eggs and sperm, contain 23 different chromosomes Fertilization,

the union of the two sex cells, produces an individual with 46 chromosomes—23 pairs The two corresponding (or *homologous*) chromosomes of each pair possess the same spots at which genes are located, these spots are known as *gene loci* Hence, each individual carries thousands of *pairs* of genes done up very neatly into pairs of chromosomes

It does not follow, however, that each individual carries two identical genes at each gene locus The two genes may be the same, or they may be different A person with blue eyes, for example, almost certainly carries two similar genes at the responsible locus these genes are those whose action leads to the production of the blue eye color A person with brown eyes, on the other hand, may carry two genes which are alike, each leading to the production of brown pigment, or he may carry one gene for brown eyes and one for blue Since an individual carrying one gene of each type is brown eyed, we refer to the gene for brown eyes as the *dominant gene* dominance is a frequent but not a necessary property of one of the forms (alleles) of genes at a given locus The gene for the blue eye color is a *recessive* gene

In the shorthand of genetics we say that there are two types of *homozygous* individuals in the case of genes for brown and blue eyes, these are the individuals who carry two representatives of the same gene—*BB* or *bb*, where *B* is the gene for brown eyes and *b* is the gene for blue There are also *heterozygous*—*Bb*—individuals who carry one gene of each sort As far as the genes for eye color are concerned, homozygous individuals produce only one type of sex cell since both members of the chromosome pair carry the same gene Heterozygous individuals, on the other hand produce two types of sex cells in equal numbers since at meiosis half of the sex cells will get a chromosome with gene *B* while the other half will get a chromosome with gene *b*

At fertilization sperm and eggs unite at random, that is, there is no tendency for sperm of one kind to seek out preferentially eggs of that or any other kind Consequently, in the progeny of two heterozygous brown eyed individuals (*Bb*), the chances of a child being brown eyed are three times as great as

the chances of its being blue eyed (Figure 4) If a heterozygous individual, *Bb*, marries a blue-eyed partner, *bb*, and they have a number of children, half of these will be heterozygous (*Bb*) and half homozygous (*bb*) This is a statistical expectation in small families, there may be only brown eyed (*Bb*) children, or only blue-eyed (*bb*) children, or some of both types but not necessarily in equal numbers

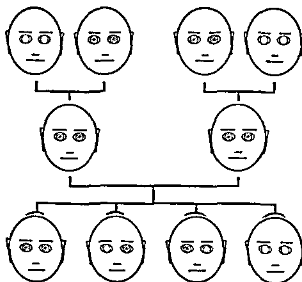


FIGURE 4 Mendelian inheritance in three generations of the blue (light) and the brown (dark) eye colors The blue is a recessive and brown is a dominant character Some brown-eyed persons are heterozygous as shown by the fact that some of their children may have blue eyes

The principle that we have been considering is that discovered by Mendel in 1865 but not appreciated by the scientific community until rediscovered independently by three different investigators in 1900 Mendel discovered the principles, or laws, of heredity (now known as Mendel s laws) not by observing inheritance in man but by crossing varieties of the garden pea. However, the basis of heredity is, most remarkably, the same throughout the

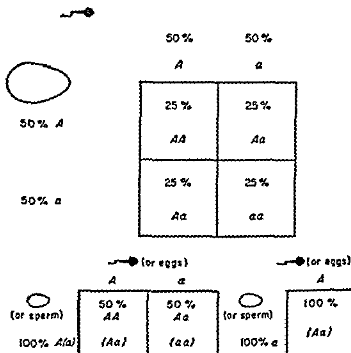


FIGURE 5 This is the first of a series of "checkerboard" diagrams, such diagrams are useful for illustrating the frequencies with which certain genetic endowments will occur The upper part of the diagram illustrates the frequencies with which offspring of various genotypes are formed following the mating of two individuals heterozygous for the genes *A* and *a* Each parent produces sex cells of which half contain the gene *A* and the other half *a* This fact is represented by the division of the top and left sides of the square into equal segments The eggs and sperm unite at random, this is illustrated by the subdivision of the large square into four smaller ones of equal size The offspring of this mating, then are ¼*AA* ½*Aa* ¼*aa* These proportions can be demonstrated in the progeny of a single pair of flies by the kernels on a single ear of corn, or by the matings of other organisms, in the case of human beings and other less productive organisms the same frequencies can be demonstrated by the summation of the progenies of many couples

The two smaller diagrams in the lower part of this figure illustrate the relative proportions of offspring following the mating of (1) a homozygote with a heterozygote and (2) two dissimilar homozygotes.

to peas apply also to fruit flies to man and even in modified form to bacteria and other microorganisms

To recapitulate Mendelian inheritance in man and in other higher organisms is predicated on the following phe nomena (1) The possession of *pairs* of genes by every individual (2) The occurrence of *meiosis* during the formation of the sex cells At meiosis the chromosomes (and the genes) ***segregate*** so that each sex cell carries one member of each pair (3) For any one gene an individual may have either two identical alleles (in which case we say he is *homozygous* for that gene) or the two gene members may differ somewhat (the individual is *heterozygous*) (4) As far as their gene content for a given locus is concerned all sex cells produced by an individual may be identical or half may be of one sort while the other half are of a different sort (5) Sperm and eggs unite at random during fertilization (see Figure 5)

Virtually all of the higher forms of life are equipped with pairs of chromosomes rather than sets of single chromosomes as some lower organisms are We saw above that a person carry ing the genes B and b is brown eyed the gene for brown eyes (B) is said to be *dominant* to the *recessive* one for blue eyes (b) Many recessive genes are harmful to their carriers when homozygous persons carrying both the recessive gene and its normal dominant counterpart are spared this harm There are many known recessive genes whose action in the homozygous condi tion leads to death or to the most pathetic deformities Fortu nately most of these are so rare that two persons carrying genes for the same abnormality are by the operation of chance alone unlikely to marry Occasionally however they do and it is for the guidance of such couples that heredity clinics are being established at many of the larger hospitals and medical schools

Mendel s Law of Gene Recombination

The fact that genes segregate at meiosis has a number of consequences the most important of which is the variety of

genetic endowments capable of being transmitted by an individual heterozygous for several genes So great is this variety that perhaps no two persons (except identical twins) have ever had the same genotype

We have already seen that during the formation of sex cells in man the 23 pairs of chromosomes characteristic of every body cell are reduced to 23 chromosomes One member of each of the *original 23 pairs was originally contributed by the individual s* mother while the other member was contributed by his father So among the gametes being formed, there is one type containing entirely paternal chromosomes There are 23 different types of gametes in which all of the 23 chromosomes but one are of paternal origin Similarly there are 253 different combinations of 21 paternal and 2 maternal chromosomes Without listing all *the combinations of paternal and maternal chromosomes which* are possible we can simply say that over 8 million different combinations of paternal and maternal chromosomes are possible if these chromosomes are treated as indivisible units

Actually, even this is an oversimplification There are exchanges of genes of paternal and maternal origin within individual chromosomes during meiosis If these are taken into account in computing the number of possible gene combinations any individual can produce one gets a tremendous figure—a figure so large that no two of the billions or trillions of sperm produced by any man during his lifetime are likely to contain exactly the same combination of genes It is almost certain that no two individuals (barring as stated above identical twins) have ever in the course of mankind s existence had the same genotype It is from this wealth of material and through differences in the number of offspring produced by persons with *different gene combinations* that natural selection molds the genetic composition of human populations This process lies at the bottom of evolution evolution is an inescapable concomitant of life itself

3

Spontaneous Mutation

Heredity and Mutation

Heredity is a conservative force It tends to make offspring resemble their parents If heredity were perfect, all living individuals would be exactly alike—and exactly like the first form in which life existed The fact that they are not alike indicates that the force of heredity is sometimes partially overcome by another force which induces change in the hereditary materials —in the genes This latter force is *mutation* In the preceding chapter we saw that genes reproduce themselves, that is, they cause the synthesis of copies of themselves from nongenic materials present in the cell, and ultimately from the food the organism consumes But occasionally the process of copying goes wrong and the new gene formed is not quite like the original Such imperfect copying is known as *gene mutation*, and it is the source of variation, of individuality, and of evolution It is because of mutation that some people have blue and others brown eyes, some have O type blood and others A type or B type, some enjoy good health and others suffer from thalassemia Of course, some of these mutations may have occurred many generations ago, some may have occurred only once, others may have occurred repeatedly

Genetics is a science whose very existence depends upon observable differences between individuals If the individual members of each species were identical, if every man were precisely the same as every other man, we would still have the sciences of physiology of developmental morphology, of biochemistry, and of taxonomy (Perhaps scientists in these fields would even be extremely happy, individual differences and idiosyncrasies are nothing but a source of trouble as far as they are concerned!) We would still have doctors of medicine dentists, pharmacologists and optometrists but we would have neither genetics nor geneticists In order to trace patterns of [illegible] ance we must have recognizable differences to trace

[illegible] rrent in genetics a gene is a [illegible] ound in a double helix, [illegible] xed order, simple chemical structures called [illegible] pens that there exist only four kinds of nucleotides commonly found in chromosomes How can four kinds of nucleotides make up the countless different genes which exist in the living world? The answer seems to be that the *sequence* in which these four kinds are arranged within the gene serves as a code much as do the holes in the tape or cards controlling modern business machines The code embodied in the arrangement of nucleotides within a gene determines just what the gene will do There are many different ways in which a thousand objects of four different kinds can be arranged to supply each gene with its unique code and, hence, with its unique function

Gene mutation is, then, most easily imagined as resulting from a mistake in the coded sequence of nucleotides within the gene An error, perhaps that occurs during chromosome duplication consisting of the loss of a few nucleotides or of a change in their position relative to one another Or an error caused by the collision of a chemically highly active molecule, such as a peroxide or a free radical with the chromosome At any rate, whatever the cause a gene that has been performing one function occasionally ceases to function, functions at a different rate or functions in an entirely different manner

The mutated gene, during the course of subsequent gene and chromosome duplications reproduces itself in its altered

form There is no known process by which DNA can correct a mistake of this sort, once it has occurred, except by chance back mutation, an event as rare as or rarer than the original error Blue eyes or brown, black hair or blonde or red, blood types A, B, or O—all of these well known differences between persons have their origin in these errors in gene reproduction and are expressed as obvious differences because of the effects these changes have on the physiological functioning of genes

Mutation in Man

Mutational changes in any one gene are (with infrequent exceptions which we need not consider here) rare events This is a different way of saying that, ordinarily, the genes reproduce themselves accurately Mutations were first discovered by the Dutch botanist Hugo de Vries soon after 1900, in a plant called the evening primrose (Oenothera) Beginning about 1910 T H Morgan and his associates observed and described many mutants in several species of Drosophila Since about 1945 the phenomenon of mutation has been studied extensively in bacteria and in other microorganisms, in which, with the aid of proper methods many billions of individuals may be rapidly screened for the occurrence of mutations

Although man is not a favorable subject for studies on mutation, it is certain that mutations do occur in man and ingenious methods have been devised for their investigation One of these is referred to as the "direct method Consider, for example a fairly common type of dwarfism in man in which the head and the trunk are of normal size but the limbs are abnormally short If persons afflicted with this condition—chondrodystrophia—survive early childhood, they enjoy reasonably normal health as adults but are obviously handicapped in many kinds of work This type of dwarfism is inherited as a dominant trait That is children who are chondrodystrophic dwarfs are usually born in families in which at least one of the parents is also such a dwarf We may say that the dwarfism is due to a dominant gene *D*, while the normal body build is caused by the

corresponding recessive, *d*. The dwarfs are heterozygotes, *Dd*, and normal people homozygotes, *dd*.

It does happen occasionally, however, that both parents of a chondrodystrophic dwarf are of normal stature. The normal recessive gene *d* evidently mutates to the dominant gene for dwarfism, *D*. To determine the rate of this mutation, many thousands of birth records must be surveyed. One scores the number of dwarf and normal children and then checks the parents of every child in the survey, removing from his data those children whose parents (one or both) were dwarfs. The remaining children born of normal parents, would consequently be expected to be normal too. However, in one such study made by a Danish geneticist, it was found that about one child in 12,000 born to normal parents was afflicted with this type of dwarfism. Since the normal parents did not carry the dominant gene, these children must represent new mutants. In each instance, the mutation could have occurred in either the gene supplied by the mother or in that supplied by the father; since 12,000 children represent 24,000 genes (at this one gene locus, remember), the mutation rate is 1:24,000, or approximately 0.000,04. In other words, about four per hundred thousand sex cells produced by normal people carry a newly arisen mutant gene for chondrodystrophic dwarfism.

The "direct method" of determining the frequency of mutation is applicable only to dominant traits, since the emergence of a recessive trait (such as the blue eye color) in the offspring of parents manifesting only the dominant trait (brown eyes) simply means that the parents carry the recessive gene in heterozygous condition. The frequency of mutation toward recessive genes which produce recessive hereditary diseases or malformations can sometimes be estimated with the aid of the "indirect method."

Let us take as an example hemophilia, or bleeders' disease, which is produced by a recessive gene located in the chromosome that is also concerned with the determination of sex. The blood of hemophiliacs does not clot, and so even small cuts and abrasions may result in fatal hemorrhages in these persons. In fact, only a fraction of all infants who are born with hemophilia reach

maturity, the remainder die in childhood Nevertheless, new hemophiliacs are born in every generation, almost always to parents with no blood disease How is this possible? One might think that a gene which kills most of its carriers would soon eliminate itself from the population We are forced to make one of the following two assumptions First we may suppose that the supply of hemophilia genes in human populations is renewed in every generation by the occurrence of new mutations If, then, the number of hemophilia genes removed by early death is approximately balanced by the number of newly arisen mutants an equilibrium is established at which the chance of a child being born with hemophilia remains roughly constant generation after generation On the other hand, it can be imagined that the present frequency of hemophilia genes represents only a residue left over from higher frequencies existing in the past. This second assumption is demonstrably absurd It would imply, for example, that Hannibal s army and the Roman legions that opposed him were composed mostly of hemophiliacs History has certainly failed to record any such condition

We are left, then, with the assumption that for hemophilia and similar hereditary diseases, there exist, in human populations approximately stable equilibria between the elimination of harmful genes by death or sterility and their origin by mutation Knowing the proportion of hemophiliacs who survive to adulthood and produce children of their own, one may calculate the frequency of new mutations that must occur to maintain the equilibrium Such calculations have been made by J B S Haldane and other geneticists for a number of disease producing genes in man The results are fairly consistent in giving mutation rates ranging from 1 10 000 to 1 100,000 Mutation rates determined by the ' direct method ' also fall within this range

Measurement of Mutation Rates in Drosophila

Man is an intractable, expensive, and unreliable animal to work with when it comes to studies of mutation rates The

amount of time, labor, and money needed for census-taking examination of old records, and the tracing of families for personal interviews is often prohibitive Consider that to obtain reasonably reliable information about the rate of mutation of a gene that mutates only once in 100,000 sex cells, we must examine birth records for at least 250,000 children. It is no wonder, then, that the best data concerning mutation rates are obtained from organisms suitable for experimental work in laboratories

The availability of a prolific laboratory animal, large numbers of which can be raised in a short time, does not in itself guarantee that reliable data can be obtained Such data come more often from the use of efficient techniques, such as those developed in the mid twenties by H J Muller For perfecting these techniques and for vigorously pursuing the lines of investigation they opened—especially in the field of radiation genetics—Muller was awarded a Nobel Prize in 1946 Not only because an understanding of these techniques will be essential later in this book but also because of their intrinsic interest, we shall consider them here in some detail

We have seen that the mutation rates for individual human genes are generally very small To obtain information about these mutation rates, one is faced with the necessity of studying extremely large numbers of individuals If one wishes to study *differences* in the rate of mutation of different genes, or the possible effect of some physical or chemical agent on the mutation rate of a particular gene, the numbers of individuals required for the study become prohibitively large—even for a small animal such as the fruit fly Indeed, in refined studies of this type, the investigator can no longer be satisfied with rough estimates of mutation rate It becomes necessary to amass sufficient data to guarantee that the observed rate of mutation is correct within very narrow limits

Muller's method of keeping the experimental errors to a minimum and, at the same time, keeping the amount of work within feasible limits was extremely clever (One must remember that thirty or forty years ago the amount of money available for genetics and other "useless" research was even more limited than

it is today, only a few of the larger universities could afford such luxuries) Muller saw the necessity of studying mutation rates, not in single genes, but in groups of genes carried in the same chromosome A chromosome may contain hundreds or thousands of genes If there were some aspect of development that was affected in a similar way by many of these genes, and if all these genes could be held together and analyzed as a single unit, the over all mutation rate—the frequency with which *at least one* of these many genes mutated—would be relatively great And if the over all rate were considerable, proportionately fewer observations would suffice to obtain an accurate estimate of this frequency Muller reasoned further that the most common gene changes and the ones most likely to occur in many different genes, were lethal changes Lethal mutations are those which alter development (in this case, of the fruit fly) so drastically that the mutant individuals die In human terms, lethal genes produce hereditary diseases or malformations grave enough to cause the death of affected individuals before the advent of adolescence and sexual maturity

The use of lethal mutations for studies of mutation rates has a further advantage It eliminates what is sometimes spoken of as the personal equation of the investigator Suppose, for example, that we are looking for mutants which alter the color of the Drosophila fly s eyes Some of these mutants are so conspicuous that everyone will notice them for example, a commonly used mutant has white instead of the normal dark red eyes But there are also mutations which change the eye color so slightly that a careful examination is needed to detect them And the fact of the matter is that some observers can perceive slight changes in color more easily than others This makes comparisons of the data obtained by different observers unreliable, and even the same observer may overlook more mutants when he is tired than when his attention is at its keenest The experiments with lethal mutations, on the other hand are contrived so that one has to examine and score not individual flies but *cultures* of flies for the presence or absence of an entire, clear-cut class visibly distinct from other classes in the same culture, a class of flies that should be represented by at least several dozen

individuals Even a novice can make accurate observations of this sort For the first time, then, different investigators could perform studies of mutations and arrive at comparable results Scientific literature dealing with problems in this field became a meaningful body of knowledge, from which one could proceed into unexplored fields without repeating old experiments merely *in order to evaluate one's own ability to perform this type of work*

The frequencies of mutations observed in experiments using Muller's techniques are, of course, much larger than those mentioned above for human material As stated above, the reason for this is that one determines the probability that at least one of a great many genes will mutate One particular chromosome in the common fruit fly, for example, mutates from a lethal free condition to one in which it carries a lethal gene at rates varying from 1 1,000 to 3 1,000, depending on the strain of flies studied Another chromosome of the same fly, one that is about twice the size of the first, acquires a lethal mutation at a rate of about 5 1,000, that is, about 5 of every 1,000 sex cells produced by a fly contain a newly arisen lethal mutation in this chromosome It was by using this technique of measuring the frequency of lethal mutations in entire chromosomes of Drosophila that Muller was able to prove that mutations occur more frequently *in the progenies of flies irradiated with x rays than in flies not subjected to such treatments This topic will be discussed in more detail in Chapter 5 For the time being,* we are concerned with "spontaneous" mutation, that is with mutation which occurs in flies or other organisms not subjected to any known mutation inducing treatment "Spontaneous" mutation must surely have a cause, and calling it "spontaneous" means simply that we do not know what that cause is

Mutation Rates per Gene

How can the mutation rates determined per chromosome in Drosophila be compared with the rates per gene estimated, as

discussed above, for some genes in man? This is a difficult and highly technical problem, but we must acquire at least a very general idea of its solution What is needed here is an estimate of the numbers of genes carried per chromosome in a favorable experimental animal such as Drosophila

We have stated that there are hundreds or even thousands of genes in each chromosome In genetically well studied organ isms, such as Drosophila, dozens or even hundreds of genes have been identified by the changes they produce in the char acteristics of the organism when they undergo mutation These are, however, only a fraction of the total number of genes pos sessed by the organism This total number can be estimated by studying the genes whose alteration leads to similar end results

We have seen that white eyes can arise in a number of genetically different ways in Drosophila There are even more mutations that result in the death of individuals carrying only the mutant gene and not its normal allele If we collect a num ber of these lethal" mutations, each of which is known to have had an origin separate from that of all others (that is, each has been obtained through mutation from a different, lethal free individual), we can ask how often *the same* (allelic) gene muta tion has been obtained two or more times by chance Obviously, the greater the number of different genes that give rise to 'lethal mutations, the smaller the chance that any two will be the same In fact, the frequency with which two such mutations prove to be identical is equal to 1 divided by the number of places where the mutation can occur This type of test indicates that there are at least 500 different gene loci in one chromo some in Drosophila that can yield lethal mutations For a variety of technical reasons, this is known to be a minimal estimate, more probable estimates lead to the conclusion that there are some 1,000 genes in that chromosome or about 5,000 genes in the entire chromosome complement of this fly

As stated above, the rate of origin of new lethal mutations in a certain chromosome of the vinegar fly, *Drosophila mela nogaster*, is about 5 per 1,000 chromosomes per generation, or 0 005 Since this chromosome contains at least 500 genes capa ble of producing lethal mutants, the rate of mutation per gene

is 0 005 divided by 500 or 0 000 01 (1 per 100 000 genes per generation) It is remarkable that this estimate agrees with the value obtained for human genes (see page 37) If as is probable the Drosophila chromosome actually has more than 500 genes Drosophila genes would have to be considered somewhat less mutable than human genes

These figures may also be compared with those obtained from various microorganisms such as the common colon bacillus the pink bread mold and bacteriophage (a virus that is parasitic on bacteria) Using organisms such as these one can study enormous numbers of individuals on a culture plate four inches in

TABLE I

Examples of mutation rates per gene per generation in various organisms (10^{-3} or 10^{-6} means that approximately one individual per thousand or one individual per million acquires a newly arisen mutation in a given gene in every generation for further explanation see text)

Organism	*Mutation rates* *From*	*To*
Bacterial virus (bacteriophage)	10^{-9}	10^{-3}
Colon bacillus	10^{-9}	10^{-5}
Indian corn	10^{-6}	10^{-4}
Drosophila (fruit fly)	10^{-7}	10^{-5}
Man	10^{-5}	10^{-4}

diameter more individual bacteria can be grown than there are human beings on the face of the earth By using special techniques involving agents such as antibiotics that kill normal bacteria it is possible to determine the frequency with which mutant *resistant individuals arise* The range of mutation rates determined in this way extends from 0 000 01 or higher values down to values of 0 000 000 000 1 (from 1 per 100,000 to 1 per 10 billion cell generations)

Some mutation rates found in a variety of organisms are shown in Table I The table suggests that there is a general tendency for mutation rates to increase as one moves from viruses and bacteria toward the higher organisms However some mutation rates in lower organisms are as high as those

listed for Drosophila or man Of course these are the mutation rates per generation the length of a generation in man is about 25 years in Drosophila about the same number of days while in bacteria and bacteriophages it is estimated in minutes If we were to estimate the mutability per unit of time the genes in bacteria would prove to be most mutable and those in man least mutable

On the other hand it is possible that the data for man are biased in the direction of giving higher estimates than they should If one were to use the direct method outlined above in the search for mutations occurring in man with a frequency of 1 to 10 billion sex cells per generation (as in bacteria) and if one were to limit the study to children born in the United States (at a rate let us say of 150 million per generation) one would have to accumulate data for 350 generations or roughly 10 000 years in order to observe about 10 such mutations Small wonder that mutation rates of this sort have not been found in man! But with bacteria a study involving mutation rates as low as this can be made conveniently within a period of 48 72 hours

In addition to the limitations imposed on an investigator of human populations by the number of individuals he can handle there is a further limitation imposed on his estimates of mutation rates Without casting aspersions let us say simply that people will be people and that there is a certain amount of infidelity in this imperfect world The frequency of uncon trolled and uncontrollable conceptions establishes a base line beyond which studies of mutation rates cannot go except by the severest limitation of the types of material studied—a limi tation that restricts even further the number of persons available for study

Chromosome Mutations

Thus far we have restricted our discussion to mutations of which most

Another kind of mutation involves breakage and reunion of chromosomes which as we know are the gene carriers Chromosome mutations are important genetic consequences of radiation exposure (see Chapter 5)

A chromosome like a piece of string may be broken into two or more pieces Such accidents happen to chromosomes only rarely under ordinary circumstances but the frequency of chromosome breakages is increased by exposure to atomic radiations and to certain chemical treatments A cell in which one or more chromosomes have been fractured is in a precarious situation To carry on its normal functions indeed to remain alive a cell generally needs all the genes it normally contains Few if any genes are dispensable The cell needs its full complement of chromosomal material Now as shown in Chapter 2 during cell division the chromosomes divide and one complete set of chromosomes moves into each of the daughter cells This movement is however not a property of the whole chromosome it depends upon one spot in the chromosome which contains a specialized body called the *centromere*

Consequently when a chromosome is broken one of the pieces—the one without the centromere—lacks the ability to migrate to its appointed place when the cell divides. As a result, one of the newly formed cells does not get its full quota of genes and generally dies However unlike a string a chromosome possesses sticky raw ends wherever a break occurs If two of these ends meet they will rejoin and the break will be healed Consequently when a single break occurs there are two possible outcomes Either the one piece is lost at the next cell division as mentioned above or prior to the division the broken ends meet rejoin and restore the chromosome to its normal condition Other possibilities arise if two or more breaks occur in a cell simultaneously One or more of the chromosome fragments may be lost and the cell may die or the breaks may heal and the original chromosomes may be restored Two chromosome fragments which lack centromeres may join or two fragments both including centromeres may join cells in which this happens are not viable The piece of one chromosome lacking a centromere may join the piece of the other chromosome with a centromere and the other pieces may also join thus forming

two new chromosomes containing one and only one centromere each

Such new chromosomes, which contain blocks of genes previously carried in different chromosomal bodies, may function in a perfectly normal way in ordinary cell divisions Genes are sufficiently independent in their action to produce a normally viable and healthy *organism even if reshuffled between different* chromosomes As a matter of fact, some of the cells in an adult body do not divide at all, and fragmentation of their chromosomes need not destroy their ability to live and to carry on their functions We shall see later that this fact throws light on such important problems as destruction of cancer cells by x rays or radium treatments, and radiation sickness produced by the exposure of the body to excessive amounts of high energy radiation

Mutation and the Welfare of the Organism

We have stated above that gene mutation can be visualized most readily as a mistake in the chemical pattern of the gene which arises during the process of gene reproduction A mutant gene is essentially an incomplete, imperfect, defective copy of the parent gene Now, the genes which an organism carries are there not by a lucky *accident but because of the slow, steady,* unrelenting process of fitting or adjustment to the environment in the course of evolution Genes in healthy, vigorous human beings, or for that matter in healthy and vigorous mice or flies or corn plants, are really masterpieces of biological evolution You would hardly expect a masterpiece, such as a painting by El Greco or Rembrandt, to be improved if some dauber took it upon himself to change it Mutation spoils a gene much more often than it improves it for exactly the same reason And yet, one should not jump to the conclusion that mutation can never improve the gene After all, the paintings of El Greco and Rembrandt were improved—in fact, they were created—by the brush strokes made by their authors

But let us set aside the analogies and look at the facts Among the mutants in Drosophila the largest and most easily

detected group are the recessive lethals which kill their carriers when homozygous Moreover, just as there are countless diseases hereditary and otherwise, which kill men, so there are many ways a lethal can kill a fly About 5 to 10 percent of the lethals kill embryos before they have left their egg cases about 80 per cent kill during the larval stages the remaining 10 to 15 percent kill pupae or young adults while they are emerging from their pupal cases

In addition to lethals, there are mutations that simply lower the chances of a fly attaining adulthood Some of these muta tions are associated with externally visible effects (almost all of the mutations used by geneticists in their studies are of this sort), others are not Very few of these semilethal or subvital mutants have distinct intermediate effects that is, a gene muta tion affecting development generally kills all or almost all flies carrying it, or it has a much more subtle effect which results in the death of a relatively small percentage of its carriers Just why some individuals live and some die when they carry these semilethals is hard to tell Perhaps variations in the severity of the environment are responsible just as in man some persons afflicted with a hereditary disease may die while young, others at a later age, and still others may live and even enjoy fair health

The mutants of Drosophila which are pictured in textbooks of genetics or of biology are mostly defective in some way or another The white eyed mutants have lost the eye pigment that normal flies have and with it have lost their visual acuity Wing mutants usually make the wings less serviceable for flying or reduce them to useless vestiges A mutant that makes the fly yellow instead of the normal brown might seem to have caused no appreciable harm, and yet yellow males are less successful in mating with females than are males of normal color

However, these textbook mutants' are apt to convey a false impression They are a selected lot—selected because they produce sharp, easily visible easily scored changes The more radical the change, the less likely it is to be harmless, not to speak of its being useful Yet mutants do occur which make the fly a tiny bit larger or smaller, develop a little faster or more slowly, have slightly more or fewer bristles on certain parts of

the body, deposit on the average slightly more or fewer eggs Some of these unspectacular mutants sometimes called *poly genic* ones, may be neutral or even favorable The evidence for this comes from studies on populations of flies living in their natural habitat The individuals in such wild' populations differ from one another in just such polygenic traits, and the only way in which this normal variation could have arisen is by mutation Similarly, with normal people, some are taller and others shorter, some have darker and others lighter hair or eyes some exhibit differences in facial features which are diffi cult to describe in words but are easily perceptible to us as the recognition marks of our friends

Useful Mutants

Gene structure is evidently capable of multitudinous modi fications and some of these chiefly those which produce minor alterations in the characteristics of the organism may be innoc uous or even useful and may become incorporated into the array of genotypes we describe as normal for the species Moreover, and this is important, it is often the environment which deter mines whether a given mutant is harmful or useful Diagram matically clear examples of this can be cited especially in micro-organisms We have already mentioned mutants in bacteria which are resistant to antibiotic substances that kill normal bacteria. Are these resistant mutants good or bad for the bac teria? It stands to reason that they are good in an environment containing the antibiotic, for in such an environment the non mutants are unviable However, nature did not make a mistake when it evolved bacteria that are sensitive to these drugs In drug free environments the sensitive varieties often enjoy vari ous advantages which the resistant varieties do not have The latter may be more fastidious in requiring various nutrient substances not required for growth by the former It is known, for example, that some of the streptomycin resistant mutants do not

grow at all except on nutrient media containing streptomycin What was a poison to "normal" bacteria has become a necessity to the resistant strain

Breeders of agricultural plants and animals are always on the lookout for mutational changes of possible economic usefulness Since the mutation process is speeded up by high energy radiations (see Chapter 4), the possibility arises that among masses of worthless mutants there may be found a few useful ones Ake Gustafsson, a Swedish plant geneticist, is the pioneer in this type of work, which more recently has been taken up by some other breeders in various countries Table II lists some

TABLE II

Some useful mutants obtained in the progeny of plants exposed to high energy radiations (after Brock modified)

Plant	*Description of mutants*
Barley	Dense spike, large grains broad leaves, tall and short, stiff straw, high yield
	Improved malting quality
	Higher protein content
Wheat	Resistance to black stem rust
	Increased yield, stiff straw, increased grain weight increased tillering, improved baking quality
Oats	Increased yield
	Stiff straw, increased grain weight
	Rust resistance, improved quality
Peas	Increased yield, more branches, more pods, later maturity
Soybeans	*Early ripening*
	Increased yield, shortened internodes, increased branching, more pods, increased seed weight, *earliness*
Flax	*Increased yield of long fiber*
	Rust resistance
Jute	Increased fiber yield and quality
Peanuts	Increased yield and disease resistance
Oil turnip	*Earliness, faster seedling growth*
	Increased yield

examples of radiation induced mutants in various agricultural plants that may prove serviceable in breeding work

The existence of these useful mutants certainly does not contradict the statement made above that a mutant gene is usually a more or less defective copy of the gene from which it arose In the first place the mutants listed in Table II are a tiny residue selected from a much greater mass of mutants most of which were discarded because they were useless or harmful Second consider the fact that any agricultural plant exists in what is a new environment—new compared with the environ ments in which the plant lived before man began cultivating it Finding useful mutants among agricultural plants is no more surprising than finding bacteria resistant to antibiotics among billions of bacterial cells exposed to selection by antibiotics that kill off all the nonmutant individuals

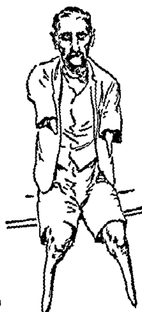
Adaptive Value of Human Genetic Variants

In the case of man we are familiar with the common gene mutants that for all practical purposes seem harmless The eye color genes mentioned several times serve again as an example So too do the genes which are responsible for the different blood types of different individuals *thanks to the existence of* blood banks most of us have become familiar with the blood types AB A B and O and with Rh positive and Rh negative Skin pigmentation hair form and color shapes of ears and noses degree of hairiness and many other common differences be tween persons are known to have a relatively simple genetic basis Most of these variations make no great difference to a person s health

But one should not jump to the conclusion that these gene-controlled variations are absolutely neutral and under no circumstance make any difference to their possessors You may have learned from your blood bank whether your blood is rhesus positive (Rh+) or rhesus negative (Rh—) This is important information because it has been found that a serious—often



(a)



(b)



(c)



(d)

FIGURE 6 Examples of mutant genes in man, which produce hereditary diseases defects, or malformations (a) progressive muscular dystrophy, (b) acheiropodia (absence of hands and feet), (c) achondroplastic, or chondrodystrophic, dwarfism, (d) xeroderma pigmentosum (abnormal freckling and light sensitivity of the skin), (e) ichthyosis congenita (leathery skin with deep, bleeding cracks a usually lethal condition)

(e)



(f)







(g)



(h)

(f) syndactyly (fusion or absence of fingers) (g) brachydactyly (one-jointed fingers) (h) harelip (failure of the two halves of the upper jaw to fuse properly) For purposes of illustration, we have selected mutants which produce drastic and easily visible changes in their carriers, it should be kept in mind that many mutants cause only slight variations, of the sort in which "normal' persons often differ

fatal—condition of newborn infants is caused by the occasional interaction of a baby s blood with that of its mother

The abnormal condition known technically as erythroblastosis fetalis, is evoked ordinarily by an unfavorable combination of paternal, maternal, and offspring genotypes The gene in question has two forms *Rh* and *rh*, *RhRh* and *Rhrh* individuals have Rh positive blood (The *Rh*, incidentally, is an abbreviation for rhesus monkey and is used because blood from Rh positive persons will react with blood serum obtained from a rabbit that has been previously injected with blood from such a monkey) Individuals homozygous for the *rh* gene (*rhrh*) have Rh negative blood A man and wife who are Rh positive and Rh negative, respectively, may have children who are all Rh positive, or half may be positive and half negative During pregnancy there may be a leakage of blood from the developing embryo into the mother s blood stream, and vice versa If the child is Rh positive his blood carries into his mother s blood a protein which to her body is strange, her body manufactures antibodies to fight this protein just as it would to fight any infection Apparently the amount of leakage is not great, at any rate, the first Rh positive child—and even the second and third—may be born in a perfectly normal condition There comes a time during a later pregnancy, however, when the *developing child is Rh positive and the mother has* built up enough antibodies to cause trouble Because of placental leakage, some of the mother s blood finds its way into the embryo Here the maternal antibodies find the strange protein they are designed to fight Unfortunately, this strange protein happens to be in the red blood cells of the unborn child These cells are largely destroyed, and after birth when the baby must rely on the red cells to transport oxygen to different parts of his body, his blood does not function properly At present the lives of some such babies can be saved by means of total transfusions—replacement of all the blood in the infant s body

The origin or erythroblastosis fetalis is an illustration of the general principle that common and apparently innocuous gene differences may become quite important under certain circumstances Evidence *is growing that not only* the Rh blood

types but also the better known A B O system of blood group genes may differentially predispose their carriers to certain ail ments Thus persons with the O blood type are slightly, but significantly, more frequent among sufferers from duodenal ulcers than they are in the general population

TABLE III

Some mutations in man

Disease	*Description*	*Mutation rate* ($\times 10^{-6}$)	*"Health"*
Achondroplasia or chondrodystrophia	Short limbed dwarfs high mortality during early childhood affected women bear children by Caesarean section only	10–70	0 10
Epiloia	Tumor like growths on many organs such as brain skin liver heart lungs and kidney relatively few individuals survive to 30 years of age	8–12	Very low
Retinoblastoma	Malignant tumor of the eye which necessitates removal of the eye ball immediately (early childhood) one fifth of those affected must have both eyes removed	20	Below normal
Dystrophia myotonica	Muscular disorder resulting from disorders in the nervous system	8	0 30
Marphan s syndrome	Long slender fingers and toes displaced lenses in the eyes frequent heart disorders	5	0 50
Aniridia	Absence or defect of iris resulting in seriously impaired vision	5	Below normal
Hemophilia	Inability of the blood to clot	25–50	0 25

Not all mutations in man have as subtle an effect as do the *Rh rh* genes in bringing about erythroblastosis fetalis In Table III we have listed a number of the better known human hereditary defects along with a description of their effects, their estimated mutation rates and an indication of the health of the affected individual as measured by his ability to leave surviving offspring Most of the conditions listed are semilethal or worse,

fatal—condition of newborn infants is caused by the occasional interaction of a baby's blood with that of its mother

The abnormal condition known technically as erythroblastosis fetalis, is evoked ordinarily by an unfavorable combination of paternal, maternal, and offspring genotypes The gene in question has two forms *Rh* and *rh*, *RhRh* and *Rhrh* individuals have Rh positive blood (The *Rh*, incidentally is an abbreviation for rhesus monkey and is used because blood from Rh positive persons will react with blood serum obtained from a rabbit that has been previously injected with blood from such a monkey) Individuals homozygous for the *rh* gene (*rhrh*) have Rh negative blood A man and wife who are Rh positive and Rh negative, respectively, may have children who are all Rh positive, or half may be positive and half negative During pregnancy there may be a leakage of blood from the developing embryo into the mother's blood stream, and vice versa If the child is Rh positive his blood carries into his mother's blood a protein which to her body is strange her body manufactures antibodies to fight this protein just as it would to fight any infection Apparently the amount of leakage is not great at any rate, the first Rh positive child—and even the second and third—may be born in a perfectly normal condition There comes a time during a later pregnancy, however when the developing child is Rh positive and the mother has built up enough antibodies to cause trouble Because of placental leakage, some of the mother's blood finds its way into the embryo Here the maternal antibodies find the strange protein they are designed to fight Unfortunately, this strange protein happens to be in the red blood cells of the unborn child These cells are largely destroyed, and after birth when the baby must rely on the red cells to transport oxygen to different parts of his body his blood does not function properly At present the lives of some such babies can be saved by means of total *transfusions*—replacement of all the blood in the infant's body

The origin or erythroblastosis fetalis is an illustration of *the general principle that common and apparently innocuous* gene differences may become quite important under certain circumstances Evidence is growing that not only the Rh blood

price of having to care for some defectives? Such a danger, if it exists at all, is remote. In the first place, we could not, at the present level of our knowledge, bring the mutation process to a halt even if we wished to do so. The issue before us now is that of mutation becoming more frequent. Second, the amount of genetic variability—the raw material of evolutionary change—available in human and other sexually reproducing populations is amply sufficient to sustain a great deal of further evolution; we shall see later that in any one generation the contribution of mutation to this store of variability is infinitesimal compared with that which has already accumulated within a species.

This last point deserves some further comment. S. S. Chetverikov, one of the pioneer geneticists, said that a sexually reproducing species is like a sponge, absorbing mutants as they occur. Human individuality—the fact that every person has a unique, unprecedented, and nonrecurrent genotype—is a consequence of the perpetuation of the genetic variability that has arisen by mutation. However, genetic variants that, in combination with other genes carried by the organism, lead to vigor and good health are perpetuated in populations rather more easily than are detrimental genes. Not that the latter are absent—we shall see in Chapter 6 that populations do carry "genetic loads." Nevertheless, the variety of genes present in sexually reproducing populations does represent a store of genetic raw material from which adaptive changes can be constructed in the process of evolution. Lack of genetic variability for further evolution of the human species is something we need not worry about.

4

Atoms and Radiations

Life and Radiation

The sun and its life giving rays have inspired wonder and awe in men of every age sun worship was a part of many religions Here are some lines from the *Hymn to the Sun* composed by Ikhnaton, a pharaoh of Egypt, more than three thousand years ago

> *Thou art he who createst the man-child in woman,*
> *Who makest seed in man,*
> *Who giveth life to the son in the body of his mother,*
> *Who soothest him that he may not weep,*
> *A nurse even in the womb,*
> *Who giveth breath to animate every one that he maketh*

Ikhnaton was right life endures on earth because living matter is adapted to capture and to store within itself some of the solar energy that reaches the earth Life has existed on earth for perhaps two billion years, it has learned to carry on, literally and metaphorically, under the sun" As was pointed out in Chapter 1, until man started to use the energy of atomic fission, every bit of energy he consumed came ultimately from solar radiation

But there exist other kinds of radiations in nature which are weak or absent in the sun's rays when the latter reach the earth's surface Some of these radiations are destructive to biological organization Outstanding among these destructive agents are the radiations variously called *ionizing, penetrating, short wave,* or *high energy radiations,* which are produced by radium and other *radioactive* substances Man has learned to create them artificially, some of them are generated in the processes of atomic fission and fusion

It would be out of place in this book to discuss the physical nature of radiations in detail Such discussions can be found in a large number of books written on different levels of physical and mathematical sophistication For our purposes we must, however, be familiar with some facts concerning different kinds of radiations, their measurement, and the amounts man encounters in the natural environment, and in the environments created by our modern industrial civilization

Molecules and Atoms

The world about us is composed of countless types of substances, some solid, others liquid, still others gaseous Numerous words in our vocabulary are names of these different substances —*water, alcohol, kerosene, salt, sugar, soda, aspirin,* etc. We recognize these substances by their consistency, color, smell taste, by their effects on ourselves or on things or processes in our environment. These properties and effects depend largely on the molecular structure of the substances concerned If we take a lump of sugar and divide it into smaller and smaller pieces we still have sugar left after each division until we arrive at very small units called molecules If a molecule were to be magnified about 100 million times, it could be conveniently represented by a picture on a page If a lump of sugar weighing one pound were to be magnified 100 million times it would be almost as large as the earth

Molecules can be broken into still smaller parts For ex

ample, if we heat sugar we get two quite different substances—namely a black residue of carbon and—although we may not see it as it boils off—some water The water given off when sugar is heated is exactly the same as that coming from the faucet above the sink, and the carbon is exactly the same as that found in a piece of charcoal or in soot Water can, in turn, be broken down into two further substances If an electric current is passed through water, two gases—hydrogen and oxygen—are produced Again, the oxygen and hydrogen we get from water are precisely the same as those obtained from air or other substances

What we are left with when we break apart different sorts of molecules is a relatively small number of *elements* There exist many thousands, perhaps millions, of different kinds of molecules, but they are made up of only about 92 naturally occurring elements, and even some of these are quite rare in nature How does an element differ from a molecular compound such as sugar or water? As we have seen, sugar and water can be decomposed into simpler substances quite easily But even if an elementary substance, such as carbon or oxygen or iron, is divided again and again, it still remains carbon oxygen, or iron The ultimate particle of an element, the atom, defies subdivision by ordinary maltreatment A molecule of sugar is composed of 6 atoms of the element carbon 6 atoms of the element oxygen, and 12 atoms of the element hydrogen The properties of sugar are determined by the number and relative position of these atoms within the molecule Molecules can be broken into atoms by heat, by electric currents, or by reactions with other substances Atoms cannot be broken by such manipulations The word *atom* means 'indivisible in Greek

The picture of the world composed of a fairly small number of indivisible and immutable atoms has the virtue of great simplicity and clarity Moreover, this picture is adequate for most purposes of practical life and even of rather advanced technology During the second half of the nineteenth century and the early years of the current one, most physicists and chemists thought that atoms were, indeed the ultimate reality of the material world That this conception was erroneous became clear through the discovery, by Pierre and Marie Curie, of an

extraordinary element called radium This amazing substance was found to emit, continuously and without any outside source of energy, powerful and penetrating radiations, and to transform itself, slowly but inexorably, into a quite different element—namely, lead Atoms thus proved to have a complex internal structure, and atoms of one element were shown to be capable of turning into those of another

Anatomy of the Atom: Radiations

The atoms of the 92 elements known before 1940, and a few more discovered since then, can be regarded as consisting of three basic particles—*electrons*, *protons*, and *neutrons* These particles are extremely small—10 000 times smaller in diameter than the atom itself Moreover, the interior of the atom resembles, of all things, the solar system In the center there is the atomic nucleus compounded of protons and neutrons, the nucleus may be likened to the sun in the solar system In the space around the nucleus, and spinning around it like the planets around the sun, are a number of electrons The number of orbital electrons is characteristic for atoms of each element.

The simplest atom is that of the element hydrogen A hydrogen atom has a diameter of about 0 000 000 005 of an inch The center of the atom is occupied by the nucleus the nucleus contains but a single proton, which is an electrically charged particle positive in sign Rotating around the nucleus is a single electron The electron is also electrically charged, but its charge is negative, thus balancing the positive charge of the nucleus. The mass of the electron is, however, very tiny—about 1/1 840 of that of the proton Most of the weight of the atom is thus concentrated in the nucleus Atoms of other elements are more complex Their nuclei contain varying numbers of protons and neutrons depending upon the element, and many electrons gyrate around the nuclei in fixed orbits For each element the number of electrons balances the number of protons in the nucleus Thus, an atom of one of the heaviest elements, uranium,

has a nucleus compounded of 146 neutrons and 92 protons 92 electrons spin around the nucleus in several concentric shells Atoms of other elements range in complexity and in weight between those of the lightest element hydrogen and up to and beyond uranium at the upper end

If the properties of electrons are to be studied easily they must be removed from the atoms containing them One of the early tools used for this purpose by physicists was the Geissler tube a glass tube from which most of the air has been evacuated Inside at each end of the tube is a metallic plate connected to the poles of a high voltage source of electricity by a wire that pierces the glass When the current is turned on the tube gives off a glow which is caused by the passage of a stream of elec trons through the rarefied air The electrons can be demon strated to leave the plate connected to the negative pole and to jump across the tube to the plate connected to the positive pole By coating the positive plate with a phosphorescent substance (zinc sulfide) one is able to discern the impact of the electrons as pinpoints of light

In 1895 a German physicist W K. Roentgen discovered that hitherto unknown radiations were coming out of Geissler tubes The properties of these radiations seemed mysterious enough for them to be called *x rays*— x designating the un known nature of the rays X rays are invisible to the human eye but they can be detected by photographic plates strangest of all x rays easily penetrate screens of black paper and other materials completely opaque to ordinary rays of light

The penetrating powers of x rays made them important in ways which were not obvious to their discoverer and to many others They became indispensable tools for the diagnosis of many diseases and for the treatment of some of them Well equipped hospitals and even doctors and dentists offices now usually include x ray machines Unfortunately together with properties useful to man these rays proved to have when im properly used some sinister ones as well They can cause severe damage to the body and as we have known since 1927 to the units of heredity the genes

X rays are not streams of electrons escaping from the Geiss

ler tube, electrons cannot pass easily through glass or heavy paper X rays are a part of the radiation spectrum, of which visible light is one part and radio waves still another The properties of radiation depend upon the length of its waves As shown in Figure 7, radio waves vary in length from several kilometers to a few meters, microwaves (radar waves) from meters to millimeters, infrared (heat) waves from about a millimeter to 8/10,000 (8×10^{-4}) of a millimeter visible light occupies the narrow band from 8×10^{-4} to about 10^{-5} of a millimeter ultraviolet from 10^{-5} to 10^{-6}, while x rays extend

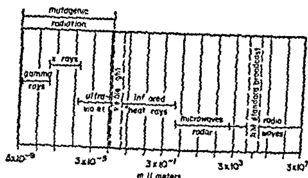


FIGURE 7 Diagrammatic representation of the spectrum of electromagnetic radiations Proceeding from the left each division represents a tenfold increase in wavelength the distance from crest to crest of the wave Visible light occupies only a small portion of the spectrum of radiations smaller in fact than that shown

from some 10^{-6} (soft x rays) to 10^{-8} (hard x rays) and to 10^{-9} (known also as gamma rays) Still shorter wavelengths (those characteristic of cosmic rays) are known

Another basic fact of radiation physics is that radiation behaves as if it comes in discrete packages, these are called *quanta* Each quantum of radiation has in it a certain amount of energy, the shorter the wavelength of radiation the greater the energy contained in its quanta Thus, a quantum of visible light has relatively little energy, quanta of ultraviolet light are more powerful, and those of x and gamma rays are more energetic still This is why x rays and gamma rays are known as high energy radiations

Effects of Radiation on Matter

When visible light falls on a material body the light quanta are either absorbed in or reflected from the body The energy carried in the quanta of visible light is however not sufficient to affect the structure or behavior of most atoms Quanta of light resemble peas shot from a toy gun against a wall the peas bounce off and do not go through the wall Only some few substances are phosphorescent This means that when they are exposed to light electrons are displaced in their atomic orbits and the substance gives off a glow (that is emits visible light) for a short time after the exposure stops The visible radiation is emitted as electrons return to their normal position Other substances such as silver bromide which is used in photographic film are light sensitive their molecules undergo chemical changes because of the energy delivered to them by light

X rays gamma rays and other high-energy radiations have quanta so powerful that they may perhaps be likened to bullets shot from a rifle When such a quantum hits an atom its energy is imparted to one of the electrons circling around the atomic nucleus An energized electron may be ejected from an excited atom and fly at an enormous speed into surrounding space where it hits other atoms Now an atom that has lost one of its electrons has lost one unit of negative electric charge It will therefore be a positively charged atom or a positive *ion* Such ions are chemically much more active than electrically neutral atoms they will react easily with other atoms or atomic groups which are able to share an electron with them

The electron ejected from an atom darts through the surrounding space where it may collide with other electrons in neighboring atoms These other electrons may in turn be knocked from their orbits A hit by a powerful x ray quantum thus produces a whole series of agitated electrons and ionized atoms The disturbance caused by the initial hit gradually subsides as the energy of the absorbed quantum is distributed among more and more electrons Finally no one electron has enough energy left to displace other electrons and the residue

of the energy is dissipated as heat By then, however, a number of electrons may have been displaced from their atoms the atoms that have lost electrons are left behind as positive ions the displaced electrons or the atoms that have picked them up are negative ions Each displaced electron results in a pair of ions, one positive and one negative This is why high energy radiations are also called ionizing radiations

Absorption of quanta of high-energy radiation by atoms is not the only cause of ionization High speed electrons, called *beta rays,* exist within x ray tubes in fact x rays are produced when these electrons strike the metal in the positive electrode Disintegrating atoms also eject electrons from their orbit at a high speed beta rays are in fact, a characteristic emanation of disintegrating radium atoms These rays have a wide range of velocities and, hence, of characteristic energies Although more energetic beta rays are known, most of those produced by atomic disintegration are capable of passing through only thin layers of aluminum or about 15 feet of air They slow down rapidly as they collide with other electrons their initial energies are rapidly dissipated by ejecting these other electrons from their orbits Again, the result of irradiation by beta rays is the formation of many pairs of ions

Since they are simply rapidly moving electrons beta rays are electrically charged Another type of charged particle is the *alpha particle,* a rather ponderous particle bearing two positive electric charges it is in fact, the nucleus of a helium atom Again velocities of alpha particles vary according to their source, a value of about one twentieth the speed of light is not unusual For all their weight, alpha particles are not efficient penetrators a sheet of paper suffices to stop most such particles However, in living tissue the extent of their penetration is not negligible, especially if their source is inside the body Throughout the distance they do penetrate, their effect is tremendous, as they roar past and through atoms, they knock electrons out of their orbits at a tremendous rate Not only electrons but even whole atoms may be dislodged by the blows of these relatively massive particles

Neutrons have effects of their own Neutrons, it may be recalled, together with protons make up atomic nuclei When

atomic nuclei disintegrate neutrons are quite frequently ejected These may travel at a fast or slow speed Since they have no electric charge they can rush or drift right through the elec tronic orbits of other atoms Eventually they are captured by the nuclei of these other atoms For reasons that are not com pletely known certain numerical combinations of protons and neutrons are unstable atoms having such unstable combinations undergo spontaneous nuclear disintegration

This disintegration or *fission* may result in the ejection of additional neutrons If as in the case of uranium 235 the aver age number of ejected neutrons is larger than 1 there are more free neutrons after the disintegration of each atom than before It thus becomes possible to initiate and sustain a chain reaction This reaction may be slow and controlled (as in atomic piles) or almost instantaneous and of great violence (as in atomic or fission bombs) Electrons are also frequently expelled from unstable atoms as high speed beta particles Furthermore the jos tling of electrons in their orbits because of nuclear adjustments frequently results in the ejection of a quantum of gamma radi ation Gamma rays are as we have seen above very powerful x rays Thus the disintegration of radium atoms results in the release of all three kinds of radiation—alpha beta and gamma rays These rays are all ionizing and the gamma rays have in addition tremendous penetrating powers

The disintegration of atomic nuclei poses a novel type of biological problem since the atoms involved change from one chemical element into another Thus upon capturing a neu tron an atom of common sodium disintegrates into an atom of iron plus an atom of helium The *isotope* (variety) of iron produced in this process is unstable and quickly changes into neon It is obvious that such changes if they occur in a living cell may result in grave disturbances Suppose that a physio logical reaction depends upon the presence of sodium atoms if some of these atoms suddenly change to helium and neon the normal course of the reaction will be disturbed The existence of a radioactive isotope of phosphorus poses a special problem for hereditary materials The desoxyribonucleic acids (DNA) which are the most important constituents of the chromosomes contain a great deal of phosphorus If a radioactive variety

phosphorus becomes incorporated into chromosomal DNA, the affected molecule of DNA is doomed Radioactive phosphorus exists for a few days only, and then changes into sulphur, an element entirely unsuitable for the chemical constitution of DNA

The normal flow of life processes depends upon the presence, in the proper place and at the proper time, of certain chemical molecules This is especially true of the processes of heredity A change in a single gene molecule in the sperm or in the egg cell may make the difference between a normal child and a pitiful invalid High energy, or ionizing, radiations disrupt the physical structure of atoms and initiate novel chemical reactions The addition of a hydrogen atom here, its loss there, the ionization of a formerly uncharged atom, the production of hydrogen peroxide, the physical disruption of long, chainlike molecules—these and a dozen other effects or immediate after effects of radiation may raise havoc with the cell s basic organization In many instances, of course, the damage is done to an expendable substance and is repaired by the cell s built in defense mechanisms In many other instances, however, damage is done to a unique substance not easily replaced or repaired Here the effects of radiation are serious There is no more unique, no more important, no more complex substance, nor one less capable of being repaired, than DNA—the chemical that conditions the hereditary processes and directs the manufacture of enzymes and proteins in every cell of the body

Measurement of Radiation

The effects of radiation upon a living cell or a living body depend upon the amounts of energy the living substance absorbs from this irradiation It is obviously important to measure the quantities of radiation applied and to relate them to the biological effects produced Thus, exposure of the body to high energy radiations may result in radiation sickness and in death (see Chapter 5), we must know, then, how much radiation of a given kind will be fatal to a mouse, or to a man, or to some

other organism We must also know how great are the amounts of radiation to which people are exposed from fallout products of testing atomic weapons, from x rays used in medical practice, and from other sources

The most useful unit for measuring exposure to x or gamma rays is the *roentgen,* usually abbreviated as ' r " It is so named to honor the discoverer of x rays One roentgen corresponds to the amount of x or gamma radiation which produces about 2×10^9 ion pairs per cubic centimeter of air This meas urement is made fairly easily with the aid of an apparatus (dosimeter) which measures the leakage of electricity from a charged object The amount of leakage depends on the number of ionized molecules, the greater the amount of x rays, the greater the number of ions, and the greater the loss of electric charge through leakage

The number of ions produced by a given amount of radia tion is, however, different in different types of substances One roentgen of x rays yields for example, about $1\ 8 \times 10^{12}$ ion pairs per gram of living tissue The measurement of types of radiation other than x and gamma rays is more involved The basic unit of the radiation absorbed is the ' rad The absorption of 1 rad delivers 100 ergs of energy per gram of matter The relative biological effectiveness of 1 rad of alpha rays is, however, approx imately equivalent under certain conditions, to that of 10 rads of gamma rays In practice, the biological effects of these radia tions are measured by equating them with effects produced by a given dose of x rays as measured in roentgens Thus we have a unit called ' rem (= roentgen equivalent for man) For measurement of very small amounts of radiation there are ' millirads (mrad one thousandth of a rad) and millirems (mrem, one-thousandth of a rem)

Sources and Amounts of Natural Radiation

All life is continuously exposed to high energy radiations Such ' natural," or background, radiations are present every where, though their intensity is generally very low There is

every reason to think that such radiations occurred on earth no less abundantly in the past, in fact, we do not know whether the first form of life arose because or in spite of radiation. It would probably be impossible, or at any rate very difficult, to create an environment completely free from such radiations

Some of the sources of natural radiation are external others are internal, within living bodies By far the most omnipresent among the former are cosmic rays These, as their name suggests reach the earth from outer space At the earth's surface cosmic rays consist chiefly of extremely high energy quanta corresponding to wavelengths considerably shorter than those of

TABLE IV

Exposure to cosmic rays in mrad per 30 years in different countries (after the report of the U N Scientific Committee on the Effects of Atomic Radiation)

Place of observation	*Mrad per 30 years*	*Place of observation*	*Mrad per 30 years*
Great Britain	840	Japan	1 020
United States	870	Northern Argentina	600
Austria	840	Southern Argentina	840
France	720		

the gamma rays of radium So great are their penetrating powers that the amounts of this type of radiation received by all organs of the human body are uniform and practically the same out doors and inside dwellings These rays have been detected in mines a quarter of a mile or more below the earth's surface The intensity of cosmic rays varies, however, with the elevation of the locality above sea level it increases about threefold as one ascends from sea level to 10 000 feet. It also varies with geographic latitude, being generally lower in the tropics than near the magnetic poles of the earth Since we are interested in the genetic damage which radiations may produce in human populations the data in Table IV are given in mrad per 30 years of exposure This interval of time has been chosen because it corresponds roughly to the middle of the reproductive life span of modern man (the average age of parents at the time half

their total number of children have been born) The radiation exposure during 30 years is then about the average exposure per human generation

Other external sources of background radiation are radioactive elements which though in very small concentrations are widely distributed over the earth s surface The amount of radia tion received by people from these sources is however highly variable because of the uneven distribution of radioactive sub-

TABLE V

Background radiation levels (including cosmic radiation) in mrad per 30 years in some cities of the United States (measurements made during August 1957)

City	Mrad per 30 years	City	Mrad per 30 years
Harrisburg Pa	2 640	Denver Colo	4 410
Pittsburgh Pa.	2,880	Colorado Springs Colo	5 040
Cleveland, O	2 730	Grand Junction Colo	4 140
Toledo O	2,280	Albuquerque N M	3 480
Ch cago Ill	2 640	Amarillo Tex.	3 240
Madison Wis	2,590	Oklahoma City Okla	2,520
Minneapolis Minn	2 760	Tulsa Okla	2 760
Sioux Falls S D	2 850	Little Rock Ark.	3 180
Cheyenne Wyo	4 260	Memphis Tenn	2 850

stances in different rocks and different soils Thus the radioactive elements radium thorium and a radioactive isotope of potassium (K 39) occur in greater concentration in granite than in basalt and in the latter in greater concentration than in sedimentary rocks External radiation rates are lower in build ings constructed of wood than in those made of brick and in the latter lower than in those of concrete or granite Because of these variations the total radiation doses received from sources external to the body are rather different in different places Table V contains estimates made by the investigators at the Health and Safety Laboratory of the U S Atomic Energy Com mission in New York (L R Solon and others 1958) These estimates include the radiation received from cosmic rays as well as other external sources

Background radiation levels appreciably higher than those summarized in Table V occur however in some parts of the world This is particularly true of a region in the state of Kerala India and in the state of Espírito Santo Brazil where many people inhabit regions of so-called monazitic sands which contain the radioactive mineral thorium The population exposed to these high radiation levels in Kerala is estimated to number about 100 000 persons The average radiation level in Espírito Santo is around 500 mrad per year (15 000 per 30 years) while in Kerala estimates between 131 and as high as 2 814 mrad per year (about 4 000 to 84 000 mrad per 30 years) have been obtained

Minute quantities of radioactive elements occur normally as constituents of human bodies and of course of all other living creatures A certain number of atomic disintegrations occurs therefore within our bodies and certain amounts of high energy radiations are produced by these internal sources. Thus the body of a man weighing about 150 pounds contains approximately 17 milligrams of radioactive potassium (K-40) and it has been estimated that human gonads (sex glands) receive some 500 mrad of gamma radiation from this source in 30 years The presence of even smaller amounts of a radioactive isotope of carbon (C-14) exposes human gonads to about 1 6 mrad per year (about 50 per 30 years) The Report of the U N Scientific Committee on the Effects of Atomic Radiation estimates the average total dose of radiation received by human gonads from both external and internal radiation sources as 100 mrem per year or 3 000 mrem or 3 rem per 30 years

Man made Radiations

Three rem per generation may be regarded as close to the irreducible minimum of background radiation to which mankind was is and will continue to be exposed In addition to this rock bottom minimal exposure mankind is and probably

will continue to be exposed to some radiations from man made sources Among the latter, the radioactive fallout from the test ing of nuclear weapons has in recent years been incessantly dis cussed in learned articles, popular books, newspapers, and magazines, and from political tribunes It may, therefore, surprise many readers to learn that the amount of exposure from fallout products is decidedly smaller than that from less pub licized man made sources—namely, from sources used for medical and industrial programs

The story of the fallout is, very briefly, as follows The explosion of atomic bombs and superbombs generates numerous unstable and radioactive isotopes of many chemical elements Among these, strontium 90 and cesium 137 are considered most important, both because these radioactive atoms are produced in large amounts and because they decompose rather slowly, continuing to give off dangerous high energy radiations for a long time Strontium 90 has a half life of 28 years, cesium 137 a half life of 27 years The *half life* of a radioactive element is the length of time required for one half of the substance to decompose and to lose its radioactivity But after two half lives —that is, after 56 years, one quarter of the original radioactivity of the strontium 90 fallout will be preserved, after 84 years one eighth, etc Last but not least, strontium 90 and cesium 137 are important because they are absorbed and retained in the bodies of plants animals and men

Atomic explosions hurl radioactive materials high up into the atmosphere, even into the stratosphere These materials are carried aloft and then, for a certain time, transported about the earth by winds Eventually they fall once more to the surface of the earth—hence, the term *fallout* A part of fallout is local fallout, these are materials which settle in the neighborhood of the test site within a few days after the explosion But lighter particles in the upper reaches of the atmosphere and in the stratosphere may remain aloft for several years may be carried around the whole earth, and may settle only slowly—but not slowly enough to have lost their radioactivity Since most of the atomic test sites have thus far been located in the temperate and subtropical belts of the Northern Hemisphere (see Figure 8),

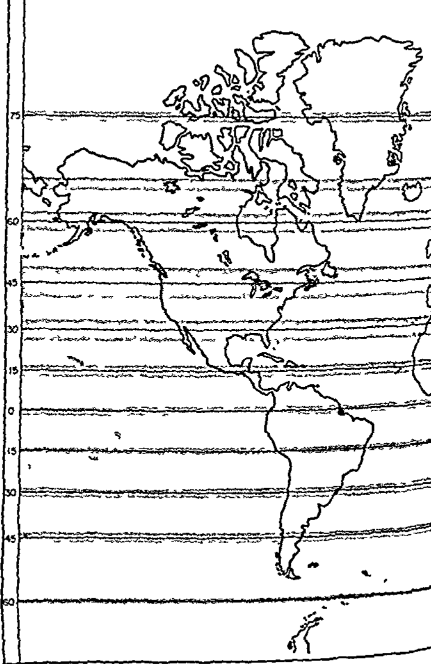
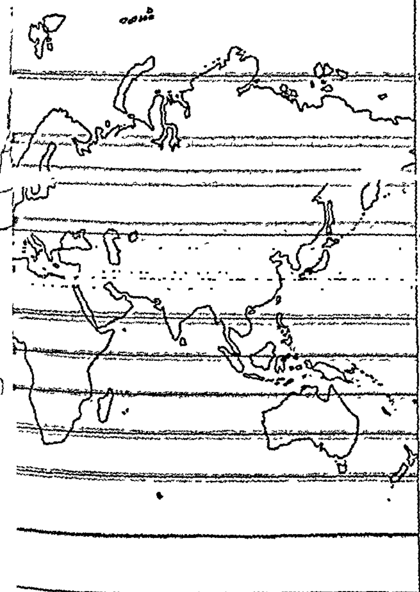


FIGURE 8 A schematic representation of world wide fallout patterns as one of the more common by products of atomic and thermonuclear explosions latitudes of the Northern Hemisphere, the lowest averages (1 or 2 microcuries erable variation which is not represented in this figure and which results from amount of fallout in a given area



these are revealed by the quantity of strontium 90 *in the soil* Strontium 9(
The highest average (about 10 *microcuries per square mile*) occurs in the
per square mile) occur *near the equator* and at the two poles There is con
local climatic conditions, *rainfall* is especially important in determining

fallout in this region has been greater than in the Arctic, along the equator, or in the Southern Hemisphere Nevertheless, fall out is a world wide problem

Some strontium 90 and cesium 137 may enter the human body through actual inhalation of air containing fallout particles By far the most important source, however, is vegetables that have absorbed fallout products from the soil, or milk and milk products from cows that have been pastured on contaminated vegetation A great deal of research in several countries has attempted to estimate the amounts of strontium 90 and cesium 137 which people accumulate, and the amounts of ionizing radiations which will reach human sex cells from these radioactive atoms Indeed, strontium 90 has made its unwelcome appearance in milk, in cereals, and in vegetables, and it can be detected in the bones of persons of various ages, the concentration being especially high in the bones of growing children The genetically significant dose of radiation from this source is, however, not easy to determine On the assumption that atomic weapons tests will not resume after the end of 1958, the average dose to human sex cells per 30 years will apparently be about 10 mrem, that is, about one third of one percent of the amount received from natural sources (see Table V) If, however, weapons tests are continued at the present rate for the next century, the exposure will be increased, in the generations to follow, some four to ten times

The radiation exposure of human sex cells through the testing of atomic weapons will, thus, amount to only a fraction of the presumably irreducible exposure to radiation from natural sources As we shall attempt to show in the chapters that follow, this does not mean that the additional radiation is negligible Moreover, if a war were unleashed in which nuclear weapons were used, the radiation exposure would be much greater than that resulting from either the testing of weapons or natural (background) sources

By far the most important source of radiation to which human populations are at present exposed is neither background radiation nor atomic bombs but the x ray machines in hospitals and in doctors' offices X rays have a very important place in

modern medical practice They are virtually indispensable in diagnosing many ailments, from toothache to tuberculosis and cancer They are essential preliminaries for many surgical opera tions Equally important is the therapeutic use of radiation Treatments with radiation are applied in cases of malignant tumors and for many other lesser ailments Radioactive sub stances particularly iodine 131, phosphorus 32, and gold 198, are given internally to some patients, usually in small quantities, and chiefly for diagnostic purposes

The unquestionably beneficial uses of radiation in medical practice are unfortunately, coupled with some attendant danger of genetic damage Genetic damage arises when high energy radiations impinge on reproductive organs This occurs to some extent no matter what part of the body is irradiated inten tionally If a beam of sunlight enters a room part of the light is reflected and scattered throughout the room Similar scatter ing occurs also with x rays and other radiations When, for example, a beam of x rays is directed at the chest of a patient to examine his lungs a fraction of the rays also reaches the sex cells This occurs even with dental x rays When x rays are directed at the pelvic region as in obstetrical examinations the gonads of the mother as well as those of the unborn child may be directly in the intense field of the primary beam

More and more persons are employed by industrial plants that use x or gamma radiations to inspect their products One reads with increasing frequency of this or that company which has obtained a cobalt 60 source of radiation for some aspect of industrial research Quality control through automatic ma chinery activated by radiation sources is becoming common place, all TV viewers are aware by now that the manufacturer of one brand of cigarettes claims greater uniformity through this type of control Finally, both in industrial and research laboratories the use of radioactive atoms has become extremely common Radioactive atoms do not differ from ordinary atoms in their chemical behavior Consequently, in the study of indus- trial or physiological chemical processes, radioactivity offers a means of tagging certain atoms and following them through a variety of reactions The technique used is basically the same

whether one wishes to determine . . . deposits . . . paras . . . For the genetic effect of radiation on human populations, it makes no difference what problem is being investigated, the increased use of radioactive isotopes means that more members of the population are being exposed to radiation

How much radiation exposure is incurred by people because of the medical occupational, and technological use of radioactive substances? This is very difficult to estimate with any precision The sources of uncertainty are many First of all, it is evident that people in technologically advanced countries are exposed to radiations more frequently than people in primitive or underdeveloped countries But even in countries with well organized research facilities it is no easy matter to find out the genetically important exposure dose—that is, the dose which reaches the sex cells. Take, for example, the radiations used to treat patients with malignant growths Even if massive doses of radiation are applied, the genetic effect may be slight, indeed, most such patients are beyond the childbearing age, and for many of them even the chances of survival are small

The Report of the U N Scientific Committee on the Effects of Atomic Radiation has collated and attempted to interpret a mass of data on man made radiation exposures in Austria, Denmark, England, France, Japan, Sweden, and the United States The figures arrived at vary from 20 to 150 mrem of exposure per year from diagnostic radiations, from 1 to 30 mrem from therapeutic exposure less than 1 mrem per year from radioactive substances taken internally, and less than 2 mrem per year from occupational exposure These are averages per person, certain individuals of course receive considerably more than others Multiplying these figures by 30 to obtain genetically effective doses per human generation, we obtain totals of 720 mrem to 5,500 mrem In other words, people in technologically advanced countries are, on the average, exposed to a total amount of man made radiation about twice as great as the average natural background (see Table V)

This trebling of the natural radiation exposure is certainly

disquieting since, as we shall see below, it is bound to produce some genetic damage Most certainly, we should not be frightened to the point of denying people the benefits which legitimate medical uses of radiation are capable of giving These benefits are too obvious and too important to be renounced But it is also certain that precautions should be taken to minimize radiation exposure, particularly of the sex cells, as far as possible This can be done by using screens made of materials opaque to x rays to shield the reproductive organs of patients as well as physicians and medical technicians Recognition of the genetic and other dangers of radiation should make us avoid unnecessary exposure It is, for example, very doubtful whether x ray machines should be allowed to be used for shoe-fitting One need not rely solely on genetic arguments to justify this statement, the growing bones in children s feet, because of the rapid division of bone cells, are especially sensitive to x ray exposure, just as are other tissues—including cancerous growths—in which cell divisions are common Solely on genetic grounds one can argue, however, that temporary male sterility should never be induced by irradiation, too many alternative and convenient techniques are available to justify the use of an agent which may doom a future individual to a life of misery and unhappiness

whether one wishes to determine what compound in gasoline deposits carbon on valves in automobile engines or what part of parasitic virus enters and kills a bacterium For the genetic effect of radiation on human populations, it makes no difference what problem is being investigated, the increased use of radioactive isotopes means that more members of the population are being exposed to radiation

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5

Induction of Mutation by Radiation

Discovery of the Speeding up of Mutation by X rays

Genes are the carriers of genetic information This fact makes them the controlling influence in determining the path which the development of an individual will follow in a given succession of environments The genes present in a fertilized egg cell can be passed faithfully to every one of the 2^{47} cells (a fifteen place figure) composing the body of an adult man as well as from generation to generation This transmission is possible because of the unique chemical properties of the DNA molecule which ensure a faithful replication of the gene pattern and also because of the wonderfully efficient organization of living matter This organization includes the consolidation of groups of genes into chromosomes and the elaborate mechanisms of cell division

It is known that penetrating or high energy radiations are destructive to biological organization Radiation striking a molecule is likely to change it from its original to a biologically abnormal condition Of necessity then radiation must threaten

the normal functioning of the genes and of the living body which is dependent on their proper action

The mutagenic (mutation inducing) effect of x rays was discovered by Muller in 1927 As described in Chapter 3 Muller realized the difficulty inherent in studies on mutation rates of single genes He solved the difficulty by treating chromosomes as units and by studying a type of mutation—recessive lethals—which occurs in many genes within a chromosome For example if there were 300 genes for each of which mutations from normal to lethal occurred at a rate of 0 000 01 the mutation rate observed for the chromosome as a whole would be 300 times 0 000 01 or 0 003 (3 lethal chromosomes per 1 000) Muller s technique made the quantitative study of mutation rates feasible

To see what the Mullerian approach accomplishes suppose that in order to prove that the rate of mutation is increased by x radiation we must obtain about 10 lethals in a control series and about 30 lethals in a corresponding experimental (x rayed) series If we limit ourselves to a study of a single gene for which the spontaneous mutation rate is 0 000 01 and for which the mutation rate under the influence of irradiation is trebled or 0 000 03 we shall have to make some 2 000 000 observations to be reasonably sure that the radiation is responsible for the increased mutation rate If however we use Muller s technique our task is to demonstrate the reality of the difference between the mutation frequencies 0 003 and 0 009 this can be accomplished by making only some 6 600–6 700 observations Since we have studied simultaneously the mutation rates of 300 gene loci our labor has been reduced 300 times An experiment that would have required a heroic effort can now be performed by one person in a matter of weeks

In Muller s classical experiments 1 177 chromosomes of Drosophila flies treated with a massive dose of x rays yielded 143 lethal mutants 741 chromosomes treated with a dose only one fourth as large yielded 59 mutants and in the control experiment in which flies were not exposed to x rays 6 016 chromosomes yielded 5 lethals The differences between the outcomes of the three series of experiments are far too great to be explained by chance alone It follows that lethal mutants are

more frequent in the progeny of flies treated with x rays than they are in the control experiment X rays are mutagenic.

Direct Proportionality between the Amount of Radiation and the Number of Mutations

Since x ray treatments speed up the mutation process, the problem that immediately presents itself is the quantitative relation between the amount of x rays applied and the frequency of mutations induced This problem was taken up by C P Oliver and by N W Timofeeff Ressovsky as well as by Muller himself Figure 9 shows some of the results obtained in X chromosomes of *Drosophila melanogaster*, the common vine gar fly Along the vertical axis in the diagram in this figure are plotted the percentages of all treated chromosomes found to be carrying recessive lethals Along the horizontal axis are plotted the various amounts of x radiation to which the chromosomes were exposed The measurement of x ray dosage, it will be remembered, is made in units designated as r (for Roentgen the discoverer of x rays), 1 r is that amount of irradiation neces sary to produce 1 8 $\times$ 10^{12} ion pairs per gram of tissue Ejecting an electron from one atom it may be recalled, results in the formation of two ions or charged particles one ion consists of the atom which has lost its electron the other of an atom which has picked up the extra electron Although 10^{12} (1 followed by 12 zeroes) is an enormous number, there remain 100 billion times as many nonionized atoms in tissue following an exposure to 1 r

The solid line of the graph in Figure 9 is drawn through the points representing experimental findings, the dotted line is a straight line obtained by correcting the observed frequencies for instances in which one expects two or more lethals to be induced in the same chromosome and, hence, to be erroneously scored as a single lethal There are three important features of this diagram (1) The corrected curve is a straight line, every increase in the amount of x rays to which the chromosomes are exposed results in a corresponding increase in the mutation rate

(2) The line starts slightly above the horizontal axis the initial height represents the spontaneous mutation rate occurring even in the absence of radiation (3) There is no known threshold below which irradiation is ineffective in producing mutations.

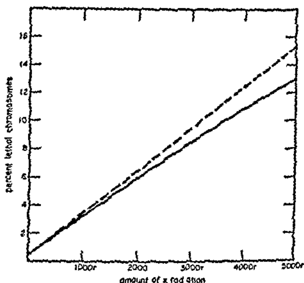


FIGURE 9 The frequency with which sex linked lethals are induced in mature sperm of *Drosophila melanogaster* (the common vinegar fly) as a result of exposure to various amounts of x radiation Sex linked lethals are lethal mutations of genes which are located on the *X chromosome* the chromosome which is important in the determination of the sex of an individual

The solid line corresponds to actual observations the dotted line which represents the direct proportionality between the frequency of induced lethals and the dosage is obtained by correcting the data for chromosomes carrying 2 or more lethals

The value of 25 r is the lowest dosage studied in fruit flies Recent studies with bacteria have been made with doses as low as 8 r, these low exposures also result in the production of gene mutations

The results of the experiments summarized in Figure 9 are very important They show that no matter how small the amount of radiation to which an organism is exposed, a certain calculable

number of mutations will be induced by it As far as the genetic effects of radiation are concerned there is no such thing as a permissible or safe amount below which mutations are not induced This could by no means have been predicted or assumed on theoretical grounds As a matter of fact many physiological effects of radiation (of which more will be said below) do not behave in this way Large amounts of radiation produce dangerous radiation burns in the exposed individuals while small amounts have no immediately detectable harmful effects In general many physiological reactions in organisms have minimal thresholds—that is quantities of stimuli below a certain minimal amount are ineffective while quantities above that minimum produce effects at rapidly increasing rates Among physiological reactions there are many instances of all or none effects as in nerve stimulation Stimuli below a certain threshold cause no discharge along the nerve fiber while stimuli slightly above or very much greater than the threshold produce equal discharges

The direct proportionality between the amount of radiation and the frequency of mutations induced has permitted a number of interesting calculations to be made It was not illogical for example to suppose that spontaneous mutations—those which occur in nonirradiated individuals—may be accounted for by cosmic and other natural radiations Physicists can measure the intensity of this omnipresent or background radiation Knowing how many mutations 1 r is likely to produce (see below) it is possible to show that considerably less than 1 per cent of the spontaneous mutations in Drosophila can be accounted for by background radiation In other words the mutations induced by radiation are superadded onto the amount which would be produced without radiation and which for a lack of knowledge we call spontaneous

Doubling Dose and Frequency of Mutation per Roentgen of Radiation

One of the ways in which the magnitude of the genetic damage produced by radiation may be expressed is based on

the amount of radiation necessary to double the spontaneous rate of mutation Turning to the data in Figure 9, we can see from the graph that an exposure of Drosophila to 1,000 r results in approximately 3 percent lethal mutations in one particular chromosome The spontaneous mutation rate for that chromosome was given earlier as 0 001 or 0 003, depending on the strain of flies used for analysis We also said that certain inferences led to the conclusion that there are about 300 gene loci at which lethal mutations can occur in this particular chromosome What is the mutation rate that would result at one locus as a result of exposure to 1 r? To calculate this, we divide 0 03 by 1,000 to get the mutation rate per chromosome per r, and we divide this answer (0 000,03) by 300 in order to reduce the calculated mutation rate to that for a single locus The answer is 0 000 000,1, *there is one chance in 10 million that exposure of a single gene* to 1 r will result in its change to a state having a lethal effect The spontaneous mutation rate per gene locus can be calculated by dividing 0 001 or 0 003 by 300, the answer in this case lies between 0 000,003 and 0 000 010 The average mutation rate per locus is somewhat less than 1 per 100,000, perhaps 3 per million is a better estimate Allowing for this uncertainty, it would appear that an exposure of flies to between 30 r and 100 r would double the spontaneous mutation rate This is a calculation based on averages for many genes, recent information obtained for various genes in bacteria indicates that the *doubling dose*—the amount of radiation required to give an induced mutation rate equal to the spontaneous rate—varies from about *16 r to* over 100 r for different gene loci Thus the information obtained from lethals in Drosophila is borne out by these more sensitive studies

Mutations in Different Organisms

A flood of confirmatory reports followed Muller's discovery that x rays increase the mutation rate in Drosophila These reports, which dealt with a wide variety of organisms both plant and animal, showed without exception that in every form

of life in which mutations could be studied radiation was effec tive in increasing the mutation rate At the present time man of all biological species of particular interest to the geneticist happens to be the only one for which there exists no completely convincing evidence that mutations are induced by radiation It would be foolish indeed to regard this as an indication that man may be immune to the mutagenic effects of radiation Experi ments involving deliberately contrived and adequately con trolled crosses are obviously out of the question in man The geneticist is thus deprived of the very techniques needed to demonstrate the induction of mutations

A great deal of effort has been expended in studying radia tion induced mutations in mice Even though some people may argue that whatever we learn about mutations in mice will be scarcely more applicable to man than what we find in Drosophila it is nevertheless desirable to check our conclusions through studies of a form of life somewhat closer to man than are flies Mice like men are higher animals—mammals Not only do they live longer than flies do but—and this may be more im portant—the processes of development and maturation of the sex cells in the ovaries and testes are similar to those in man

Techniques analogous to those devised for Drosophila by Muller and others are not yet available for mice W L Russell and his collaborators in this country and T C Carter and his colleagues in England have had to use a more laborious method A strain of laboratory mice is prepared which is homozygous for 7 recessive mutant genes these genes affect various easily visible characteristics of the animals chiefly the coat color so that it is possible to tell by examining a mouse whether it is or is not homozygous for a given gene Suppose then that a female mouse from this multiply recessive tester strain is crossed with a male from an ordinary normal wild type strain A normal mouse carries dominant variants of all the recessive genes in the tester strain Barring mutation the entire progeny (F_1 genera tion) of this cross will consist of animals heterozygous for the recessive genes received from the tester strain to which their mother belonged and for the normal dominant genes received from the father This progeny will almost always be like the

normal, wild type parent Only rarely does an individual exhibit the traits of one or another of the 7 recessive genes of the tester strain Such individuals arise when a sex cell of the normal strain (in this case a spermatozoon), happens to carry a mutant allele of one of the 7 genes of the tester strain

The experiments are divided into two parts In one, females of the tester strain are crossed with normal males In the other, the reciprocal cross, mutant males are crossed with normal females The mutations detected in the first set of experiments must have arisen in the male parent, in the second, in the female parent Moreover, some of the normal parents are treated with a known amount of radiation, while others serve as non irradiated controls Some of Russell's results are as follows

Normal parent	*Dose of irradiation*	*Offspring examined*	*Mutations recorded*
Male	None (control)	37,868	2
Male	600 r	48,007	53 or 54
Female	None (control)	40,918	0
Female	400 r	7,859	7
Female	258 r	26,468	2

Among the 48,000 offspring of irradiated fathers there were 53 or 54 mutations (one was not quite certain), while only 2 mutants were found among almost 38,000 mice in the progeny of nonirradiated fathers A total of 9 mutants appeared in the progeny of irradiated mothers, and none in the control experi ments Irradiation is clearly mutagenic in mice, as it is in flies and in other organisms We shall have occasion to refer to these experiments with mice later in this book

What Radiations Are Mutagenic?

In Chapter 4 we saw that the physical properties of radia tions depend on their wavelengths Geneticists have studied the mutagenic powers of radiations of both short and long wave-

lengths They have also studied the mutagenic powers of radia tions delivered in different ways—gradually, over periods of days or weeks, rapidly, in a matter of seconds or minutes, continu ously, or alternated with periods of "rest" Of necessity, these experiments were done mostly with fruit flies, corn, and some lower organisms

It was quickly revealed that, with x rays and other high energy radiations, it is the total dose of the radiation—the total number of roentgens (see Chapter 4) to which a gene or a chromosome is exposed—which determines the frequency of the mutations induced As shown in Chapter 4, "soft x rays have relatively long wavelengths and consist of relatively small energy quanta, 'hard x rays and gamma rays have short wavelengths and high energy quanta The hardness or softness of the radia tion has no effect whatever on the mutations induced, provided only that the radiation is able to penetrate to the sex cells The number of mutations produced is determined by the number of ionizations caused by the radiation exposure, and it is the number of ionizations that is measured in roentgens

Even ultraviolet radiations are mutagenic The relation between mutation and exposure to ultraviolet rays is, however, a complex one and need not concern us in this book Ultraviolet rays have a much longer wavelength than the softest x rays, and their penetrating powers and energy quanta are low Visible light and infrared rays are not mutagenic The term *high energy radiation* does not apply to ultraviolet and to longer wave lengths

The rate at which radiation is delivered has under most circumstances, no effect on mutation frequency With powerful radiation sources such as powerful x ray machines, radioactive cobalt, or atomic bomb explosions, massive amounts of radia tion can be delivered in a matter of seconds on the other hand, by placing flies at a distance from a radiation source, the treat ment may be prolonged for days or weeks The number of muta tions induced by a given number of roentgens is the same regard less of whether the exposure is short or long The same number of roentgens may also be delivered in a continuous exposure, or in several bursts interspersed with periods of "rest The manner

of delivery is, in general, unimportant as far as the number of mutations induced is concerned

It is easy to see what this means to man Genetic radiation damage is an insidious thing, very small radiation exposures add up, and if continued for years may amount to as much as or more than an accidental brief exposure to intense radiation Since genetic damage is cumulative, no radiation increment, however small and insignificant by itself, can be neglected. What matters is the total exposure up to the close of the reproductive or childbearing age

It should be noted that recent data obtained by Russell and his collaborators do suggest that, in mice, "chronic' irradiation (that is, delivered gradually over a long time) may be less effective in producing mutations than ' acute" irradiation (administered rapidly) It will be remembered that Russell and his group experimented with mutations affecting 7 different genes in mice (see page 86) They obtained only 2 mutants among 26,468 mice whose mothers had received chronic irradiation, whereas they observed 7 mutants among only 7,859 mice whose mothers had been subjected to acute irradiation This matter obviously needs further study

The Directness of the Genetic Effects of Radiation

Studies of the effects of radiation on mutation rates have demonstrated that the action of radiation is direct That is, if one is to study mutations induced in the sex cells, one must irradiate sex cells (or the gonads—ovaries or testes—in which these cells are produced) One cannot obtain mutations in these cells by irradiating the head of an animal, or its thorax, or its legs Radiation does not result in the production of poisons that permeate the body and, upon arrival in the gonads, produce mutations The radiation must strike at or very near the gene which mutates

The fact that the mutation inducing action of high-energy

radiations is direct suggested a 'target" theory, which was in vogue in genetics until recently According to this theory, the quantum of x radiation acts like a small bullet, when this bullet happens to hit a gene it shoots a hole in it and thus results in mutation This view proved to be an oversimplification, the action of radiation is really quite different Irradiation results in the production of highly reactive chemical substances in the cells and chromosomes However, these substances persist in the irradiated tissue for a very short time perhaps only a fraction of a second If one of these substances happens to be produced within or very close to a chromosome, it can interact with the genetic material and induce a mutation

These two theories of the mutagenic action of high energy radiations lead to very different views concerning the possibility of discovering an antidote for radiation damage If the radiation impinging on the gene acts like a stream of bullets then there is little hope of finding treatments protective against the mutations in exposed cells The theory of mutation inducing chemical intermediaries between the radiations and the genes does offer some hope an antidote, an anti mutagen, may possibly be discovered Such an antidote will perhaps be a chemical substance more likely to react with the mutation inducing substances than are the genes themselves

Somatic Mutation

In order to induce mutations that can be observed in the progeny of an irradiated individual, one must irradiate his sex cells This does not mean that irradiation of body cells is ineffective in producing mutations in them However, the mutations induced in the body cells of a parent remain confined to these cells they are not transferred to the sex cells and consequently are not transmitted to the offspring If the gonads of the irradiated individual are protected from radiation whatever mutations may be induced in his body cells are confined to the individual exposed and will not affect his progeny

It may be noted that this fact offers excellent evidence against some nineteenth-century theories of heredity and of sex cell formation (recently revived in Russia by Lysenko) These theories held that small particles from every organ and every tissue of the body migrated to the gonads, where they became organized into mature sperm or eggs In this way each individual was supposed to have obtained the genetic information needed for proper development, head particles multiplied and formed a head, eye particles located the eye properly, and so forth If this were the case, irradiation of one portion of an animal s body should result in defective particles from that part and, hence the corresponding part should be damaged in the new embryo Needless to say, no such effect has ever been demonstrated

In order to observe mutation in body cells rather than sex cells experiments must be arranged differently, as they were in a study performed originally by J T Patterson Patterson reasoned that chromosomes are reproduced faithfully at each cell division and that each daughter cell is furnished with a complete set. He was also aware that the normal red eye of Drosophila is changed to white (pigmentless) by the mutation of a certain gene Drosophila larvae have no eyes however as larvae develop cells appear which are destined to form the eyes of the adult fly These cells form eye primordia, which are transformed into adult eyes during the pupal stage

Patterson s experiment consisted of exposing normal larvae of various ages to x rays and examining the predominantly red eyes of the emerging adults for white patches The results were clear-cut White patches did appear The number of white patches increased with dosage Early exposure resulted in large patches (many cells carrying the same mutation) late exposure to radiation resulted in small patches (very few cell divisions after the mutation had been induced) Mutations then were induced at the time of exposure Genes carried by any cell of the body consequently, are subject to mutation when exposed to irradiation

It seems highly possible that this fact has a bearing on the production of at least some forms of cancer in man Evidence

particularly suggestive of this has recently been summarized by E B Lewis for a form of cancer of the blood known as *leukemia* Leukemia manifests itself in an uncontrolled multiplication of the white blood cells, it is usually fatal The frequency of leukemia is higher among persons exposed to radiation than among the rest of the population This is known to be the case among the Japanese who were exposed to radiations from atomic bombs, and it is found also among children of mothers exposed to obstetrical x ray examination during pregnancy The doubling dose for leukemia appears to be about 30 r—an amount of radiation suspiciously similar to that calculated as the doubling dose for mutations In the face of this evidence, the implication that the origin of leukemia is mutation in a cell producing white blood corpuscles cannot be summarily dismissed, although A M Brues and others have recently questioned the validity of this hypothesis

Chromosome Breakage by Radiation

We saw in Chapter 3 that the term mutation is applied to at least two rather different phenomena—qualitative changes in individual genes (gene mutations) and chromosome breakage and reconstruction (chromosome aberrations) Both kinds of mutation occur spontaneously, and, as was demonstrated in the classical work of Muller in 1927, both are increased in frequency by exposure to high energy radiations However, the relation between the amount of irradiation administered and the number of mutations observed is quite different for genic and chromosomal mutations

Although chromosomes undergo breakage spontaneously, in most organisms such accidental breakage is very rare, at least in sex cells and in the cells producing sex cells Suppose, then, that a chromosome breaks spontaneously in 1 of every 100 000 cells As stated in Chapter 3, a chromosome break may "heal", if it does not, the cell in which it has occurred is usually unviable A chromosome aberration can arise only if at least two

chromosomes in a cell are broken, or if one chromosome is broken in at least two places Only then can the broken ends reunite in new combinations With a frequency of spontaneous chromosome breakage of 1 per 100,000 cells, two breaks will appear in the same cell by chance in 1/100 000 × 1/100,000, or in 1 per 10 billion cells The number of people now living on earth is estimated to be about 2,700,000,000, hence, the number of the sex cells in which they had their origin is 5,400,000,000 If the frequency of spontaneous chromosome breakage in man is as low as we have supposed, a chromosome rearrangement of spontaneous origin enters the entire human species only once every 2 generations

Exposure to high energy radiations greatly increases the frequency with which chromosomes undergo breakage Moreover, the frequency of single breaks increases in direct proportion to the amount of radiation applied, just as gene mutation does This has been demonstrated by irradiating, for example, flower buds and then examining under a microscope the dividing cells that give rise to the pollen grains (pollen mother cells) Some hours or days after irradiation, many of these cells show one or more fragmented chromosomes The number of chromosome breaks required to produce the observed fragments can be calculated and compared with the amount of irradiation in the treatment

The proportion of cells with two chromosome breaks may be calculated by multiplying by itself the probability that one break will be induced as has been done in the example above Suppose, then, that certain radiation exposures increase the rate of breakage by 10, 100, or 1 000 times, these exposures will increase the proportion of cells containing two breaks each by 100, 10,000, and 1 000,000 times respectively The result is that the frequency of chromosome mutations in the progeny of irradiated individuals will increase very much faster than in direct proportion to the amount of radiation This has been amply demonstrated by studies on the progeny of irradiated Drosophila, as well as with experimental plants

We may now consider the effects of chromosome breakage in sex cells and in the early germ cells that give rise to the

latter For convenience, we may divide the germ cells into two groups—those which have undergone the meiotic divisions reducing the number of chromosomes from 46 to 23, and those which have not Radiation effects in premeiotic cells are com parable to those in any other system of dividing cells, a majority of the cells in which chromosome breaks occur will get into difficulties at or after the next division and will die The death of these cells is not particularly important, since it does not lead to any clinical symptoms The cells in the gonads are inde pendent of one another to the extent that each cell goes through the series of divisions and transformations leading to a func tional gamete, regardless of the fate of its neighboring cells A heavy radiation exposure is required to destroy most of the testicular or ovarial cells the loss of a few early germ cells as the result of small radiation exposures is not serious in itself—that is, this loss does not threaten one with sterility

Treatment with x rays has been used to induce temporary sterility in men as a method of birth control This practice is clearly dangerous and should be stopped Although most of the cells in which chromosome breaks have occurred die before forming mature sperm this is not true of gene mutations Muta tions induced in the young germ cells do appear later in mature sperm In the human male, mature sperm are manufactured continuously—at least several trillion of them in all Some groups of cells in the testes preserve the ability to divide, while the cells they produce by division proceed through the trans- formations—including the meiotic division—into mature sperm Mutations induced in those cells which act as the source of sperm are passed on faithfully if we may use this word, to all descendant sperm from the moment the mutations are induced

Fortunately for man, radiation exposures are rare events, and so only a small fraction of irradiated mature germ cells are actually involved in reproduction Most single x ray exposures, and the greater proportion of one s cumulative exposure, affect mature sperm cells that never achieve fertilization Conversely, sperm cells that do fertilize eggs are exposed to radiation chiefly during their early germ cell stages This is fortunate because radiation is generally much more effective in producing muta

tional changes in mature sperm than in the early germ cells The DNA in a mature sperm cell is carried in an extremely condensed package, the sperm's "head ' In this condensed form, the chromosomal material seems to be about twice as sensitive to *the induction of gene mutations as it is in cells of earlier stages* (In part this may be a spurious sensitivity, gene mutations that are deleterious to early germ cells are partially eliminated before sperm formation)

More serious than the excessive sensitivity of mature sperm cells to the induction of mutations is their sensitivity to radia tion induced chromosome breaks Because of the condensed form of the chromosomes in the sperm head, these breaks are more likely to rejoin in erroneous patterns fatal to the cell at the following division The 'following division ' for a mature sperm is the first division of the individual formed at fertiliza tion *Sperm cells with these fatal* chromosome breaks act as "dominant' lethals, egg cells fertilized by such sperm fail to develop Now, in discussing the fate of a fertilized egg we are no longer talking of cell death in the same sense in which we refer to cells abraded from the skin or plucked out with a hair We are talking of a new individual—a rather minuscule and unimposing individual at the time, but a new individual none- theless

Radiation, Carcinogenesis, and Cancer Therapy

No group of human diseases is more feared or has attracted ... the [illegible]

tumors or *cancers* The reason for this is that the fundamen[illegible] causes which bring about these most insidious illnesses have proved extraordinarily difficult to understand Although much progress has been made in cancer studies in recent years, the fact remains that the mechanisms of carcinogenesis are still largely unknown The reason we must discuss the problem of

cancer at least briefly in this book is that it is related to radia tion in two ways First, it is well known that exposure to radia tion brings with it the risk of malignant disease Secondly, the same radiation is also used to destroy or at least to depress the growth of some malignant tumors

One of the current though by no means proved, hypotheses regarding the origin of cancer is that the transformation of an ordinary, healthy cell into a cancer cell arises through one or several consecutive somatic mutations These mutations remove the cell from normal growth-controlling mechanisms and allow it to grow and divide much faster than it otherwise would A dangerous cancer is one in which the division of certain cells has gone out of control These cells multiply, develop into masses of unorganized tissue, deplete the nutritional supply of the body, and destroy the proper functioning of vital organs by mechanical displacement or by invasion and disruption The cells which are performing their proper functions reproduce at a much slower pace and are threatened with extinction in com petition with the cancer cells Evidence has been referred to above which shows that the quantitative relation between ex posure to high energy radiation and the incidence of one kind of cancer—namely, leukemia—is the same as that for radiation induced gene mutations This does not really prove that leu kemia arises by mutation, and still less that all forms of cancer arise in this way But it does show that the mutational hypothesis of carcinogenesis cannot be easily ignored It may well be that the occurrence of a mutation in a body cell is a necessary, though not in itself sufficient, condition for the development of a cancerous growth

Let us now recall that the occurrence in a cell of an unhealed single chromosome break, or of two or more breaks followed by an improper reunion of the resultant fragments, leads to the death of this cell Let us recall also that the fre- quency of chromosome breakage is augmented by exposure to radiations Furthermore, at certain times dividing cells are exceptionally sensitive to radiation damage The reason for this sensitivity is unknown, perhaps during cell division some pro- tective substances are removed from the chain of DNA mole-

cules For the purpose of cancer therapy massive doses of x or gamma rays are administered to the part of the body containing the malignant growth The rest of the body is protected by a lead shield which is opaque to the radiation used The rapidly dividing cancer cells suffer the greatest amount of radiation damage Their chromosomes are sensitive to irradiation and their breakage and rejoining into complexes with multiple centromeres or with no centromeres leads to their death Radiation is then almost a specific treatment for cancer the damage done to normal cells in the body is much less severe and because of the slow rate of replacement of most tissue cells this damage manifests itself slowly over a long period of time The body can cope with this damage much more easily than with the cancer Thus it happens that the same agency—radiation—can be both the cause of cancer and a powerful aid in its control

Radiation Illness

We have distinguished two kinds of biological radiation effects and radiation damage One kind consists of physiological or somatic effects—changes produced in the individuals or persons exposed to radiation The other kind are genetic effects which appear only in the descendants of exposed individuals This book is concerned primarily with the genetic effects however we have seen that some somatic effects such as leukemia and perhaps other malignancies may have genetic aspects if they are caused by changes (mutations) of the genetic material (genes and chromosomes) in somatic cells Such genetic aspects can be found also in other somatic effects particularly in radiation illness produced by an excessive exposure of the whole body to radiation

Short term and long term consequences of whole body exposure can also be distinguished Follow up studies of the results of explosions of atomic weapons and of some accidents to workers in laboratories and other atomic energy installations have shown that about 50 percent of adult human beings ex

posed to 400 or 500 r of radiation die of an acute illness within a few weeks. This radiation illness, or radiation syndrome, begins with nausea, vomiting, and characteristic changes in the white blood cells, whose number in the blood rapidly falls below normal Later on there appear a high fever, reddening and hemorrhages in the skin, loss of hair, misshapen fingernails, ulceration of the mouth, throat, and intestines, and finally death Those in whom the symptoms are less severe may recover after a prolonged convalescence With smaller exposures, about 100 r, only some 15 percent of the persons exposed show symptoms of a mild radiation illness, these persons recover fairly rapidly With still lower doses only transient changes in the white blood cells can be diagnosed.

The radiation syndrome can be understood if one remembers that body tissues consisting of rapidly dividing cells suffer more damage from chromosome breakage than those in which cells are dividing only occasionally Every diagnostic symptom of radiation illness involves a cell system in which the cells are constantly dividing New blood cells are constantly being formed hair grows because cells divide in the hair follicles, fingernails are the product of continuous cell division The lining of the intestine and of the mouth and throat, and the upper layer of the skin, are continuously replaced by cell division Like cancer cells, these dividing cells are acutely sensitive to radiation After 500 r of radiation enough cells are apparently destroyed to make repair impossible, and death is the consequence

An adult Drosophila can withstand irradiation one hundred times more severe than that which is lethal to man Flies so treated become sterile but they develop nothing like the human radiation syndrome Why is the fly so resistant? The answer is that in most adult insects there is very little cell division The cells in the adult body are fixed in number But there is an exception—the reproductive organs There divisions do occur, and we find that germ cells are destroyed by much lower radiation exposures than the body itself can withstand The result is sterility of the exposed fly In agreement with the same principle, fly eggs have none of the extraordinary resistance of the adult

insect These eggs are easily killed by small doses of radiation if they are irradiated very early during embryonic development while cell division is rapid

It is likewise expected that children and infants and especially embryos during early stages of pregnancy, are more vulnerable to radiation injury than adult persons are Cell division is a requisite for growth The dose of radiation lethal to children and infants is not known, but it probably lies below 400 r Irradiation of pregnant mothers may cause miscarriages or still births as well as the birth of deformed children exhibiting more or less grave physical abnormalities All this may well be related to the more numerous cell divisions occurring in fetal and infant bodies

Persons who recover from or escape radiation illness after *exposure to intense radiation, and persons who are chronically exposed to small doses of radiation, may develop* grave physical disturbances years after exposure It should be noted that chronic exposures may add up to total amounts considerably greater than 400-500 r—a highly dangerous amount of radiation if it is delivered in a single, brief exposure Note the difference between genetic damage and physiological damage—the former is additive while the latter is not Nevertheless a study of radiologists—that is, people dealing professionally with x rays and other radiations in hospitals and laboratories—has indicated that they are more likely to die of leukemia than other members of the medical profession who are not radiologists It has also been suggested that people chronically exposed to small doses of radiation age more rapidly and die younger than do other persons This, at any rate, seems to be the case with chronically irradiated mice The hypothesis that the physiological damage in these situations may be due to an accumulation of somatic gene mutations is certainly a reasonable one

The effects of irradiating localized tissues of the body should also be mentioned Radium, strontium, and certain other elements, some of which are radioactive, are preferentially absorbed and lodged in the bones The resulting irradiation of the living cells of the bone tissue and the bone marrow may result in malignant tumors of the bones bone necrosis and

anemias—sometimes as many as 10 and even 20 years after the ingestion of the radioactive materials This is what took place in the unfortunate case of a group of workers employed to paint watch dials with a luminous paint containing radium and mesothorium Because they were in the habit of moistening their paint brushes on their tongues, these people accumulated enough radioactive materials in their bones to cause severe invalidism and death Here again, the supposition that delayed onset of these diseases can be accounted for by the occurrence of mutations in the irradiated cells cannot be dismissed

Genetic and Physiologic Radiation Damage Compared

By way of summary, we may restate again the principal difference between the genetic and the physiological effects of radiation This is especially necessary since, as we have seen above, it is possible that at least some physiological damage can be accounted for by damage to the genetic apparatus of body cells—that is, somatic gene mutation and chromosome breakage Nevertheless, the damage to the body of an individual on the one hand and to his sex cells and hence to his descendants on the other, are profoundly distinct, and this distinction must be clearly understood

With physiological damage, such as radiation burns and the radiation syndrome, there exists both a minimal amount (threshold) and a critical intensity of radiation, if either the amount or the intensity is below the critical level, the radiation has no obvious effect The cellular and bodily processes involved in producing radiation burns are dynamic chemical processes affecting relatively large quantities of different molecules in a continuous cycle of formation and destruction ' Healing processes can counterbalance the effects of radiation in this type of *system provided the radiation is not too large at any* one time

With genetic damage, on the contrary, experimental results

clearly show that there is no healing process following the induction of mutations The bulk of the experimental evidence indicates that the total amount of radiation the total number of ion pairs is the only important factor neither fractionation of the exposure nor delivery of the radiation at a low rate modifies the genetic consequences Each bit of damage induced at one time is added to that which has been induced earlier There is no half damage which can be undone by virtue of a respite from exposure These facts seem reasonable on the basis of what we have learned concerning the role of DNA in heredity and the special properties of DNA that insure its accurate self-duplication At the time the data of radiation geneticists were being obtained however the results were surprising to those whose training was primarily in physiology even today many medical doctors largely because of the emphasis placed on physiology in their training find it difficult to visualize a biological phenomenon in which the ability to heal or to revert to normal is lacking

6

Genes in Mendelian Populations

What Is a Population?

Up to this point we have considered heredity as it manifests itself in individuals and in families We have discussed the laws, discovered by Mendel, which govern the segregation and recombination of genes in the progeny of heterozygous parents the interactions of heredity and environment, the origin of mutations their frequency, their effects on the welfare of their carriers, and their induction by high-energy radiation But people live in groups, in communities from the members of which individuals usually select their mates and membership in which parents bequeath to their children Such communities —tribes, castes, social classes, nations, races—bound together by a network of marriages and of common descent, are Mendelian populations We must now consider the phenomena of heredity in such populations Genetics takes on an added dimension when it encompasses populations as units

We speak of "Mendelian populations" because the word *population* has a variety of meanings both in everyday language

and in biology Thus, one may speak of a 'population" of trees composing a forest, or of a bird 'population' which inhabits this forest The population of the world is estimated to be close to 2,700 000 000 people, that of the United States consists of some 170,000,000, that of Cleveland, Ohio, is somewhat less than 1,000,000, while that of McKean, Pennsylvania is about 300 These are the numbers of persons who live in a given territory at a given time A geneticist is interested in organisms that reproduce sexually and in populations as reproductive communities—in short, in Mendelian populations

Mendelian populations have a *temporal continuity*, they exist through time The starlings in the United States, for example, comprise a population that has existed since 1890, the year these birds were introduced from Europe In man and many other species, individuals representing several generations —children, parents, grandparents, and great grandparents—may be living at the same time, and the successive generations need not be discrete In insect populations children may mate with their parents On the other hand, many organisms have but one generation per year, and the preceding generation is dead before the succeeding one reaches adulthood

In man, population structure reaches its greatest complexity Mankind—the human species, *Homo sapiens*—is the most inclusive Mendelian population, one which inhabits nearly the whole globe Its genetic unity is attested by the existence of English, German, Japanese and other war brides the convergence of immigrants from many countries on Israel, the world wide dispersal of Russian refugees, etc But even before modern means of transportation made these extensive migrations possible, there were people who wandered around as soldiers, traders, slaves, or simple vagrants and when people travel they are likely to leave some of their genes along the way However, this does not mean that people intermarry in a random manner with respect to the place where they were born A girl from Dallas is much more likely to marry a Texan than a Californian, a German, or a Chinese Mankind is, therefore, split up into geographic Mendelian populations whose boundaries are usually not sharply defined and which need not com

cide even approximately with political units such as countries or states Nor are marriages contracted at random even between inhabitants of the same state city or village Differences of language religion economic status educational background and profession erect numerous although usually not sharply delineated communities of Mendelian populations Mankind is thus divided and subdivided into smaller and smaller popula tion units the smaller the unit the closer the approach to random mating between its members

The Gene Pool of a Population

Suppose that we examine the population of some Middle town which is reasonably uniform in social economic and religious respects and find that about 49 percent of the persons in this community have blue eyes and 51 percent have brown eyes Assume that the difference between blue and brown is due to a single gene and that blue is recessive (this is not strictly correct since shades of eye color are determined by several genes and a person with greenish blue eyes may actually carry the gene for brown) Will the proportion of blue and brown eyed persons remain the same generation after generation? What proportion of brown-eyed parents will have some blue eyed children? And should for some reason all blue eyed persons leave Middletown before reaching adolescence how many blue-eyed persons will there be produced in succeeding generations? These are examples of elementary problems with which popu lation genetics has to deal

With problems of this sort it is convenient to focus our attention not on individuals but on their gametes and the genes which these gametes contain Assume that every individual member of a Mendelian population contributes to the *gene pool* (*pool* used in this sense is analogous to its use in motor pool or pooled resources not to a pool of water) of this popula tion equal numbers of functioning sex cells and assume that these sex cells combine at random in fertilization These

assumptions are not as unrealistic as they may seem to be We know that some persons have more children than others however, we are assuming here merely that brown eyed and blue-eyed people have on the average, the same number of children Nor is it too farfetched to assume that people with eyes of a given color will not select their mates preferentially according to the eye color of the latter

Suppose now that in the gene pool of the Middletown population 70 percent, or the fraction 0 70 of the total number of sex cells carry the gene *a* for blue eyes, and the remainder—that is, 30 percent or 0 30 of the total, carry the gene *A* for brown eyes (0 70 happens to be the square root of 0 49 which is the frequency of blue eyed persons in our Middletown population, why we have chosen just these figures will appear shortly) Since the sex cells of this population combine at random, the sperm carrying the gene *A* will have 7 chances out of 10 of fertilizing an egg cell with the gene *a*, and 3 chances out of 10 of uniting with an egg cell carrying *A* Similarly the sperm with *a* will have a 7 in 10 and a 3 in 10 chance of uniting with *a* and with *A* eggs respectively The results of the union of these sex cells will, accordingly, be as follows

Egg cells		*Sperm*		*Children*	
Gene	Frequency	Gene	Frequency	Gene	Frequency
A	0 30	*A*	0 30	*AA*	0 09
A	0 30	*a*	0 70	*Aa*	0 21
a	0 70	*A*	0 30	*Aa*	0 21
a	0 70	*a*	0 70	*aa*	0 49

In other words, 0 09 or 9 percent of the population will have brown eyes and will be homozygous for the gene *A* (*AA*) 0 42, or 42 percent will have brown eyes and will be heterozygous for *A* and *a* (*Aa*) and 0 49, or 49 percent will have blue eyes and will be homozygous for *a* (*aa*) Since the homozygous (*AA*) and heterozygous (*Aa*) browns have eyes of about the same color, the frequency of brown eyed and blue-eyed persons will be 0 51 and 0 49 respectively

The fundamental problem concerning us is what the next

generation will be like Will the proportion of blue eyed and brown-eyed persons change, or will it remain the same? To solve this problem, remember that the homozygotes *AA* and *aa* will contribute to the gene pool of the next generation only *A* or *a* gametes respectively, while the heterozygotes, *Aa*, will produce, according to Mendel s law of segregation, gametes *A* and *a* in equal numbers As shown above, the three genotypes *AA*, *Aa*, and *aa* occur in the proportions 0 09, 0 42, and 0 49 Therefore, the proportion of *A* and *a* in the gene pool will be as follows

$$A = 0\ 09 + 0\ 21 = 0\ 30$$
$$a = 0\ 21 + 0\ 49 = 0\ 70$$

The proportion of the genes *A* and *a* in the gene pool remains the same as in the previous generation The incidence of blue- and brown-eyed persons in the population will remain constant generation after generation Neither the dominant nor the recessive gene will increase or decrease in frequency Do not make the error which beginning students of genetics are prone to make The dominant gene does not necessarily tend to dis place the recessive nor are dominant genes or dominant traits necessarily more frequent than recessive ones

The Hardy-Weinberg Theorem

The conclusion we have reached is valid regardless of the actual frequencies of the genes in the population Consider a population in which the gene *A* has a frequency p and the gene *a* the frequency q, such that $p + q = 1\ 00$ Proceeding as before we have

Egg cells		*Sperm*		*Children*	
Gene	*Frequency*	*Gene*	*Frequency*	*Gene*	*Frequency*
A	p	*A*	p	*AA*	p^2
A	p	*a*	q	*Aa*	pq
a	q	*A*	p	*Aa*	pq
a	q	*a*	q	*aa*	q^2

The composition of the population will, therefore, be p^2 of AA homozygotes, $2pq$ of Aa heterozygotes, and q^2 of aa homozygotes. The frequency of the genes A and a in the gene pool of the next generation will be:

$$A = p^2 + pq = p(p + q) = p$$
$$a = pq + q^2 = q(p + q) = q$$

FIGURE 10 This checkerboard diagram shows the relationship one expects to find between the frequency of 2 genes in a population and the frequency of individuals of the 3 possible genotypes In principle this diagram is identical to that in Figure 5 Gene frequencies in a population need not be limited, as is that of individuals, to the three values—100 50, and 0 percent—but can assume any value, and, therefore, the dividing lines within the square have been displaced off center by an arbitrary distance

This demonstration of the constancy of the gene frequency in the gene pool of a population was first given independently in 1908 by G. H Hardy and W. Weinberg It is the basic theorem of population genetics (see Figure 10).

Random Mating

The assumption we have made above is that marriages and the union of gametes occur at random. The validity of this assumption may now be examined. "Random mating" obviously does not mean promiscuity, it simply means, as already explained above, that in the choice of mates for marriage there is neither preference for nor aversion to the union of persons similar or dissimilar *with respect to a given trait or gene*. Not all gentlemen prefer either blondes or brunettes. Since so few people know what their blood type is, it is even safer to say that the chances of mates being similar or dissimilar in blood type are determined simply by the incidence of these blood types in a given Mendelian population.

In addition to the A B O and the Rh blood group systems, there is another set of blood types called M, MN, and N, which is independent of the foregoing ones. The interest of these latter types is that the heterozygotes in this case are easily distinguishable. Group M persons are homozygous for a gene which we may call M, these are MM persons. Group N persons are homozygous for a gene which we may call M^N. And finally, group MN persons are the heterozygotes, MM^N. Neither gene is dominant to the other.

A study of 6,129 white persons of the United States population showed that 29.16 percent had M blood, 49.58 percent MN, and 21.26 percent had N blood. What is the composition of the gene pool of this population? Remember that persons of blood type M produce gametes with the gene M, N persons, gametes with the gene M^N, and MN persons produce sex cells with M and with M^N in equal numbers. Therefore, the frequencies of the two genes in the gene pool are

$$M = 0.2916 + 0.2479 = 0.5395 = p$$
$$M^N = 0.2479 + 0.2126 = 0.4605 = q$$

Now, if marriages in this population are at random with respect to these blood types, then, according to the Hardy-Weinberg

equation, the proportion of the three blood groups in the population should be

$$M = p^2 = 0.54^2 = 0.2916$$
$$MN = 2pq = 2 \times 0.54 \times 0.46 = 0.4968$$
$$N = q^2 = 0.46^2 = 0.2116$$

The predicted incidence of the three blood types coincides almost exactly with the observed incidence There is obviously random mating in the population of the United States with respect to these blood types

Gene frequencies are *not constant* from race to race In fact, races can be understood and defined best as Mendelian populations differing in the frequencies of various genes Although within each race matings may occur at random with respect to certain traits matings between races are less frequent than would be expected by chance Indeed, if random mating prevailed between races these races would fuse in a single Mendelian population Although individuals in such a population would show a great deal of genetic variability, the races would no longer exist as distinct entities Now, in a group of American Indians the incidence of blood types was found to be M = 60 00 percent, MN = 35 12 percent, and N = 4 88 percent The frequencies of the genes M and M^N in the gene pool can be calculated, as in the example above, to be $M = 0.776$ and $M^N = 0.224$ If mating were at random, the incidence of the three blood types should be M = 60 15 percent, MN = 34 81 percent N = 5 04 percent The agreement between the observed and the calculated values is again extremely close But note that the gene pool of American whites has a composition different from that of American Indians

Changing Gene Frequencies by Mutation and Selection

The Hardy Weinberg theorem shows that gene frequencies in a Mendelian population tend to remain constant from generation to generation This is, however, correct only if (1) genes do not change by mutation, (2) the carriers of different

genes are adaptively equivalent and leave, on the average, the same number of surviving offspring, (3) there is no immigration to or emigration from the population that would bring in or remove one gene in preference to the other, and (4) the population is large enough so that accidental fluctuations of gene frequencies may be ignored No population in reality satisfies these conditions completely

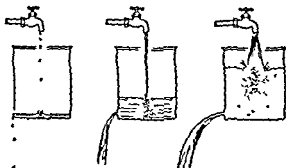


FIGURE 11 An analogy to illustrate the idea of genetic equilibrium the more water flows from the faucet into the vessel the higher the level of water in the vessel becomes and consequently the faster it escapes from the hole in the bottom Equilibrium is established when the rates at which water enters and leaves the container are equal In living populations harmful mutations are constantly produced (water from the faucet) the more frequently mutations arise per generation the greater the frequency with which they are found in the population (the level of water in the vessel) and the greater the frequency of "genetic death" (water escaping through the hole in the vessel)

We know that genes do undergo mutation, albeit usually with a low frequency such as 1 new mutant gene per 100,000 sex cells per generation Nevertheless, even such a low mutation pressure will eventually be enough to influence the gene frequency in the population Suppose that the gene *A* is occasionally converted into *a* by mutation The mutation of *A* to *a* is to the frequency of the gene *a* in a population as the flow of water from a faucet is to the amount of water in a tub in itself the mutation does not determine the final gene frequency, but

without mutation the frequency of the mutant allele would surely be zero

The final frequency attained by a gene is one representing a dynamic equilibrium, this frequency is constant (or very nearly so) not because life is static and the frequency is frozen at one level but because rates of input and outflow have become equal Using the tub analogy once more If the stopper is not placed properly water will drain out of the tub It will drain out faster as the water gets deeper and deeper Eventually the water in the tub may be deep enough to drain out as rapidly as the faucet is running the amount of water in the tub remains constant once this equilibrium is established (see Figure 11) The water in the tub is not however, the same from one minute to the next it is in dynamic equilibrium There are two forces which oppose mutation in bringing about an equilibrium of gene frequencies These are (1) back mutation of *a* to *A* and (2) natural selection Of the two natural selection is of more importance and of greater interest to us

Genetic Equilibrium

The genetic equilibrium with respect to two variant (allelic) genes in a population is reached when one of these genes enters the population at the same rate by which it leaves It enters by mutation and leaves by back mutation and by selection Let us consider some examples of selection The simplest illustration is probably that of a fatal hereditary disease caused by a recessive lethal gene Assume that the normal gene *A* mutates to the lethal *a* once in every million gametes and that all *aa* individuals die before reproducing Equilibrium is established when one individual in every million born is homozygous *aa* elimination of the gene *a* by the death of *aa* individuals then balances the origin of new *a* genes by mutation We saw above that the frequency of *aa* individuals equals q^2, therefore, q, the equilibrium frequency of the gene *a*, equals 0 001 the square root of the mutation rate (see Figure 12)

To better visualize this situation, imagine 170 persons in the population of the United States, or one person in a million, dying in each generation (25 to 30 years) from a recessive lethal mutation of this sort—an average of about 6 deaths per year in the whole country This may seem to be a very rare disease It is however, important to realize that although the number of

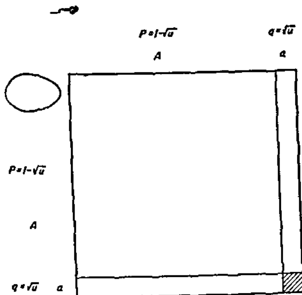


FIGURE 12 Another checkerboard one which is intended to represent the equilibrium that is established between mutation and selection in the case of a recessive lethal gene (*a*) The rate at which *a* arises from gene *A* equals *u* usually a small fraction The shaded portion of the diagram represents *aa* individuals who die because of the lethal nature of this gene Each death of an *aa* individual removes two mutant genes from the population one from the initial supply of these genes among sperm and the other from the initial supply among eggs Consequently equilibrium is reached when the shaded area equals *u* Each side of the shaded square corresponds to the frequency q of the gene *a* in the population (see Figure 10) Hence q^2 equals u or q the gene frequency equals $\sqrt{u}$ Note that the quantity q^2 is much smaller than q

homozygotes dying because of this disease is small the number of people who are carriers of the recessive lethal gene in heterozygous condition is relatively large According to the Hardy Weinberg theorem, the frequency of the heterozygous carriers is $2pq$, or $2 \times 0\,001 \times 0\,999$, or about 0 002—roughly 1 per 500 persons In a population as large as that of the United States, the number of such persons who enjoy normal health themselves but who nevertheless carry the lethal gene is about 340 000 This is about the same number of persons as the number living in Syracuse New York

The great majority of recessive genes for lethal and semilethal hereditary diseases are, thus carried not in the homozygotes who show the effects of these genes but rather in the heterozygotes who do not This fact raises a tremendous difficulty for any attempt to eradicate a recessive hereditary disease by sterilizing or otherwise preventing the reproduction of persons who are afflicted with it In the example discussed above only 170 persons show the disease in a population as large as that of the United States but there are 340 000 heterozygous carriers Since we have not discovered a method of distinguishing these heterozygotes from normal noncarriers there is little that can be done to prevent the birth of a new crop of afflicted homozygotes in every generation

As we have seen in foregoing chapters not all gene mutations are completely lethal Recessive semilethal and subvital mutants cause the death of fewer than 100 percent of their homozygous carriers in other words, some of the homozygotes manage to survive and even to beget children of their own In general, if a fraction s of all individuals homozygous for a given gene die before reproducing (or if the number of children born to such individuals is lower than the average number per couple in the population by a fraction s), then an equilibrium is established when sq^2 equals the mutation rate We can translate sq^2 as the fraction lost per homozygote multiplied by the frequency of these homozygotes in the population If we denote the mutation rate by u, we have a stable equilibrium when

$$sq^2 = u$$

$$\text{or, } q^2 = u/s$$

$$\text{or, } q = \sqrt{u/s}$$

If s equals 1—that is if all homozygotes die or for other reasons leave no children—we have the equilibrium $q = \sqrt{u}$ discussed above

To illustrate the more general relationship consider a gene *B* which mutates to *b* once in a million sex cells per generation The effect of the gene *b* is to reduce the average number of children born to *bb* parents (either to *bb* mothers or to *bb* fathers what happens when both parents are *bb* is relatively unimportant because of the rarity of such matings) to 99 percent of the average of the population as a whole The value of *s* equals then 0 01 The frequency of *bb* individuals at equilibrium will be, according to the formula above $q^2 = u/s =$ 0 000 001/0 01 or 1 per 10 000 persons in the population Within the United States there would be some 17 000 homozygous *bb* persons born in each generation or some 600 per year The frequency of the harmful gene *b* in the gene pool at equilibrium will be $q = \sqrt{u/s} = \sqrt{0\ 0001} = 0\ 01$ that is 1 percent of all sex cells will carry this gene The heterozygous carriers of this gene will amount to almost 2 percent of persons in the population $2pq = 2 \times 0\ 01 \times 0\ 99 = 0\ 0198$ or a total of 3 400 000 heterozygous carriers in the population of the United States Gathered into one place these carriers would form a city large enough to be listed among the ten largest in the world!

Genetic Death

It must be made clear just what is meant by the elimination of mutant genes from a population The symbol *s* used above stands for *coefficient of selection* This is a very important variable and its meaning demands a fuller explanation Two rather striking phrases have been used by geneticists in describing the action of selection on human populations genetic death' and genetic murder will out Genetic death encompasses, however a great deal more than death as we understand it from accounts of automobile accidents and hatchet murders

First of all, complete or partial sterility is equivalent to

complete or partial lethality as far as selection is concerned. To a geneticist, any person who dies childless is counted as genetically "dead"; that is, whatever genes he carries are, by virtue of his actions or lack of actions, removed from the population just as surely as if he had been stillborn. It is obvious, however, that the emotional impacts of death and of childlessness are in no way comparable. Second, if the mutant gene is lethal or semilethal, the actual death caused by the action of this gene can occur at any time from conception on. The loss of an individual within the first few weeks after conception is often imperceptible and, hence, causes no emotional trauma. Death at any later time, however, is recognizable as such and is accompanied by at least some degree of sadness and sorrow. We must, nonetheless, guard against rigidly equating the seriousness with which we regard the deaths of individuals and the degree of mourning or sense of loss accompanying these deaths. If there must be deaths, by all means let them occur early in development, so as to be as painless to the individual and to others as possible. But, if deaths are unnecessary, let us not develop the callous attitude that undetected deaths are of no importance. How easily this attitude can spread to encompass even living persons!

Finally, there is a perhaps unexpected property of selection that must be clearly understood. We know that many mutant genes are lethal, and that some of these cause incurable hereditary diseases which result in death only after much illness or agony. On the other hand, a subvital gene opposed by a relatively mild selection, such as we have discussed above ($s = 0.01$), may act simply by lowering the vitality of its carriers to the extent that they leave 99 surviving children where an equal number of nonmutant individuals would have left 100 offspring. At first sight, the lethal gene would seem to cause many more genetic deaths than the subvital gene. But this is not so at all. Provided that the mutation rates, u, which yield the lethal and subvital genes are equal, these genes will cause the same number of genetic deaths in the population at equilibrium.

This fact becomes apparent when we consider the implications of the equation $q^2 = u/s$, used above to describe the equi

librium frequency of mutant homozygotes in the population It will be recalled that the selection coefficient s, is equal to the amount by which the chance of surviving or the average number of offspring is reduced in homozygous individuals The net effect of the mutant gene on the population, is u/s times s the frequency of affected persons times the average adverse effect per person This product equals u, the mutation rate The conclusion is clear The effect of a recessive mutant gene on a *population* is a function of its mutation rate, and is independent of the effect as measured by the selection coefficient of the mutant on homozygous individuals This does not imply however, that the emotional impact of these various types of mutation is at all similar To watch a child suffer from hemophilia is quite different from realizing—if one could realize such things —that a child s life expectancy is destined to be one or two years less than that of his playmates

We have considered the genetic equilibrium for mutants with recessive harmful effects The situation with respect to genetic deaths is analogous for dominant deleterious mutants but the effect on the population is twice as large A dominant lethal which produces a fatal disease (such as some inherited forms of muscular dystrophy) or a subvital which produces only a slight handicap for survival or reproduction (such as brachydactyly short fingers) causes twice as many genetic deaths as there are mutations If the reader is still baffled by the equivalence of the very bad and the only mildly disadvantageous mutations perhaps the following argument will help Any harmful mutant whether its effects are drastic or barely perceptible will sooner or later have to be removed from the population in which it occurs Indeed the genetic equilibrium is a situation obtaining when the number of mutants produced is balanced by the number of mutant genes removed from the population A harmful gene that comes into a population eventually has to get out

The facts listed above have an obvious bearing on the problem of genetic damage caused by radiation in human and other populations As will be discussed in more detail in the next chapter, this genetic damage cannot be measured adequately by

taking into account only grave hereditary diseases Mutant genes with less deleterious effects result in genetic damage just as surely as the more drastic mutants

Genetic Loads in Drosophila Populations

We have seen that mutants with recessive deleterious effects accumulate in populations up to certain theoretically calculable equilibrium frequencies For example, a recessive lethal that arises by mutation once in every million gametes will have an equilibrium frequency of one per thousand in the gene pool Since, at least in higher organisms, many genes are capable of producing deleterious mutants, the gene pool of a population will contain great numbers of genes for recessive hereditary diseases, malformations, defects and weaknesses of all kinds In every generation some deleterious dominant and semidominant mutations will also be produced Since dominant genes harm heterozygous individuals, they do not accumulate appreciably in a population, they are, nevertheless, a source of ill health and misery Deleterious mutant genes of all kinds constitute the *genetic load* of a population

The magnitude and the composition of genetic loads in human populations cannot at present be estimated with any precision, although in the following section we shall consider some data relevant to this question Better data are available for populations of several species of fruit flies, Drosophila The methods used to obtain these data cannot be discussed here in detail Very briefly, they consist of taking a sample of a Drosophila population in its natural habitat and making with these "wild flies a series of crosses in the laboratory These crosses are so contrived that eventually a series of cultures is obtained each of which contains *both* a class of flies carrying in homozygous condition a certain chromosome present singly in one of the wild progenitors *and* another class of flies, recognizable by its external appearance, which carries the same "wild chromosome and also another chromosome of laboratory origin

Suppose now that a wild chromosome contains a recessive lethal The fly which in its natural habitat carried this lethal was seemingly normal because the lethal was concealed in the heterozygous state But in the laboratory culture in which a class of flies homozygous for this chromosome is produced the presence of the lethal will be evident because the class will be absent If the captured fly carried not a lethal but a semilethal a subvital or a recessive gene producing some visible abnormality in the fly's body each of these genetic variants will be detected in the test culture in which homozygous individuals have been formed The method is very sensitive if a sufficiently large number of wild chromosomes is examined one can make a census of the deleterious genetic variants that make up the genetic load of the fly population

The application of this method has disclosed that natural populations carry a large number of deleterious mutant genes concealed in heterozygous condition The frequency of these mutations will amaze many persons Let us examine the data for just one species *Drosophila pseudobscura* This species has 5 pairs of chromosomes of which 3 were examined Between 25 and 33 percent of each of these chromosomes proved to be lethal or semilethal to their carriers when homozygous Among the chromosomes that were free of lethals or semilethals between 41 and 95 percent were subvital in double dose—in other words they incapacitated their carriers perceptibly but not to the extent of being lethal or semilethal Between 4 and 14 percent of the chromosomes caused complete sterility of homozygous females and between 11 and 18 percent made homozygous males completely sterile A considerable proportion of the chromosomes made the homozygotes grow and develop more slowly than normal flies some of them as much as doubled the time required by the fly to develop from an egg to the adult stage Still other chromosomes contained recessive mutants that changed the color of the fly's eyes or body the shape of the wings etc. We can predict that a fly which is free of deleterious genes of all sorts—lethals viability modifiers sterility factors and the rest—will be found only rarely if ever

Genetic Loads in Human Populations

Since experimental methods such as those used with Drosophila are inapplicable to man, we are reduced to inference by analogy and to evidence of an indirect nature

Assume, as before, that a gene mutates to a recessive lethal state in one per million sex cells, and that its equilibrium frequency in the gene pool is consequently 0 001 Should man have as many as 10,000 gene loci capable of giving rise to such recessive lethals, there should be, on the average, about 10 lethals per sex cell or, in the average individual, some 20 mutant genes each of which is capable of killing when homozygous

This number may be an overestimate, because some—possibly most—lethals are not completely recessive but have a slightly deleterious effect on heterozygous individuals Lethals therefore do not accumulate in populations up to the frequencies expected if they were completely recessive, in studies with populations of Drosophila, it is frequently found that lethals are only half as frequent in the population as one would expect from their mutation rate If lethal genes in man behave *similarly*, there may still be as many as 5 lethals on the average per human sex cell, or some 10 concealed recessive lethals per individual

Another approach to an estimate of the genetic load in man utilizes the fact that the incidence of genetic deaths caused by mutation of a given gene is, at equilibrium, equal to the mutation rate and is independent of the kind of harm caused by the mutation If, then, the total mutation rate were known (that is, the proportion of sex cells carrying newly arisen mutants of any gene), we should have a basis *for estimating the* collective effect of these mutations on the population Estimates have been made indicating that lethal mutations represent about one fifth of all mutations which can occur at a given gene *locus* that is, for every mutation to a lethal gene there are four mutations to genes with minor deleterious effects Admitting *that we* do not know the average mutation rate to lethal genes, we may guess that it lies somewhere between 0 000,01 and 0 000 001 Assuming that man has some 10,000 genes per gamete, and mul

tiplying the mutation rate to lethals by five to obtain a measure of the total mutation rate, we may arrive at the total effect of mutation on human populations

Because of the many uncertainties involved in these calculations, the resulting estimates range from 5 to 50 percent In other words between 5 and 50 percent of the fertilized egg cells in man are "lost" through failure to develop, spontaneous abortion, miscarriage, neonatal and infant death, partial or complete sterility, and various forms of ill health L S Penrose, an eminent human geneticist, has estimated that any one generation of human beings arises from fewer than 50 percent of the individuals of the preceding generation The Genetics Committee of the National Academy of Sciences has estimated that about 2 percent of all children born in the United States suffer disorders of genetic origin Each of these estimates is compatible with our calculations, obviously, then, more reliable data are needed in this area.

Incompletely Recessive Defects

In the discussion above we have assumed that for the most part deleterious mutant genes are completely recessive to their normal counterparts (alleles), so that heterozygous carriers of these mutants are as fit and vigorous as the normal homozygotes However, as with many assumptions, this one is not always valid We must now inquire how much violence our conclusions would suffer if we gave it up Two possibilities must be examined First, that the defective mutant gene incapacitates heterozygotes as well as homozygotes, though the former less so than the latter, second, that the defective gene makes heterozygotes more vigorous than *normal homozygotes* which do not carry the gene We will discuss only the first of these possibilities in the present chapter

Suppose that a recessive lethal mutant (that is, one which kills all homozygotes) has a slight deleterious effect on the health of heterozygous individuals Perhaps the chances of reaching

adulthood are only 95 percent as great for heterozygotes as they are for persons free of this lethal, or perhaps heterozygotes produce, on the average, only 95 percent as many children as homozygous normals do In other words, the heterozygotes have a 5 percent disadvantage in survival, or in childbearing or rearing or in a combination of all these factors We may also use this 5 percent coefficient of reduction of the survival and reproductive efficiency to calculate the effect of mutant genes which are not lethal but produce various relatively minor incapacities (that is, semilethal and subvital conditions) Thus a mutant which lowers the fitness of homozygous individuals by 10 per cent may be assumed to lower that of heterozygotes by $0\ 05 \times 0\ 10 = 0\ 005$ (5 per 1,000, or 0 5 percent)

Considering each kind of defect separately, most recessive defects and hereditary diseases are rare in human populations although in the aggregate they are responsible for much misery As pointed out above, rare recessive mutant genes are carried chiefly in heterozygous individuals Even if the harm done by such genes to the heterozygote is small, it will have an overwhelming effect on the equilibrium frequency of the genes in the population We have seen that a completely recessive lethal arising once in every million gametes would reach an equilibrium frequency of 1 per 1,000 in the gene pool—one thousand times the mutation rate If, however, this lethal lowered the survival or fertility of heterozygous individuals by 5 per cent it would accumulate until its frequency were only 20 times the mutation rate—1 in 50 000 Similarly a gene with the same mutation rate which lowered the survival of homozygotes by 1 percent (these homozygotes would be 99 percent ' normal) would reach an equilibrium frequency of 1 per 100 If, on the other hand this same gene lowered the fitness of heterozygotes by 5 percent of 1 percent, or by 0 05 percent, the equilibrium frequency would be only 1 per 500 The general equation that expresses the relationship between mutation and selection for an incompletely recessive gene at equilibrium is $u = pqhs$, where u is the mutation rate, p and q are the frequencies of the normal and mutant genes respectively, h is the fraction of the mutant gene s effect which is expressed in heterozygous individuals and s is the effect of

the mutant gene on homozygotes Since the mutant gene is rare, p is very nearly equal to 1 Thus q can be shown to equal u/hs (see Figure 13)

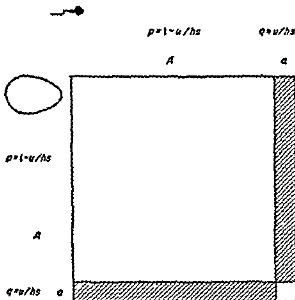


FIGURE 13 An illustration of the equilibrium that is established between mutation and selection in the case of an incompletely recessive gene First we note that the shaded area is much larger than the small square in the lower right hand corner any appreciable effect of the mutant gene on heterozygous individuals will overshadow that on the rare homozygotes the latter may be ignored in our calculations Gene a arises from A at a rate u it is lost from the population at a rate which corresponds to hs (the disadvantage of heterozygotes) $\times$ $2pq$ (the frequency of heterozygotes in the population) $\times$ ½ (since the elimination of a heterozygote removes only 1 a gene) Thus $hspq$ equals u or since p is very nearly 1 00 q equals u/hs

The gene frequencies of incompletely recessive defects would therefore be *lower* at equilibrium than if they were completely recessive In the balance sheet we have been keeping for the population, however, the adverse effect of these genes

would be *greater* than calculated before In fact, the effect of a mutant gene which lowers the viability of *heterozygous individuals* is about twice as great as that of a completely recessive gene The reason for the larger effect is that the harmful mutation will be relatively rare in the homozygous condition and will, therefore, exert its effect almost exclusively through heterozygous individuals As we saw above, the equilibrium frequency, q, for a gene which lowers the survival or reproductive ability of heterozygotes equals u/hs The frequency of heterozygotes is, of course $2pq$ Since q is very small, $p = (1-q)$ can be considered 1 This leaves the frequency of heterozygotes as $2u/hs$ The amount by which heterozygotes are affected equals hs, and the product of $2u/hs$ times hs equals $2u$

The biological meaning of these computations is that an incompletely recessive mutant gene which adversely affects heterozygous individuals lowers the fitness of the population by twice its mutation rate We saw above (page 115) that the *number* of genetic deaths produced by a completely recessive deleterious gene is equal to the mutation rate, and is independent of the degree of harm this gene produces This independence of the number of genetic deaths from the degree of harm produced obtains also for incompletely recessive mutants, but here the genetic deaths are twice the mutation rate There appears to be no easy escape, mutations will take their toll

How Much Time Is Required to Reach a Genetic Equilibrium?

Mutation rates are not necessarily constant through time There is indeed, a danger that mutation rates may go up in connection with the use or misuse of atomic energy Nor are intensities of selection constant—modern medicine, for example promises to diminish the selection coefficients of some genetically conditioned defects We have discussed gene frequencies at equilibrium and we have seen how these equilibria arise

through the opposing forces of mutation and selection the influx of gene mutations into a population and the siphoning off of these mutations by differences—sometimes slight, sometimes marked—in survival and fertility How long does it take for an equilibrium to become established? The answer to this question depends on the nature of the gene under discussion but in general it takes a long time

Let us consider once more the example of a recessive lethal that arises by mutation once in every million gametes The equilibrium frequency of this gene is 0 001 If it were possible to postpone selection until equilibrium had been established, it would require 1 000 generations or in man some 30 000 years for the frequency of this lethal to increase in a population from 0 percent to 0 1 percent the equilibrium value Selection of course does not wait and so there will be occasional homozygous individuals formed long before the frequency of this lethal reaches 0 1 percent consequently it will take much longer than 30 000 years to attain this frequency

Recessive genes with effects less drastic than complete lethality will take even longer to reach their final frequencies We have seen that in these cases the equilibrium frequency is equal to $\sqrt{u/s}$ The quantity s (the rate of selection) is usually greater than u the mutation rate Consider a mutant gene which makes the homozygotes 99 percent normal and which arises once in every million gametes Its equilibrium frequency will be 0 01 It would take much longer than 10 000 generations or 300 000 years for this frequency to be reached This is a time interval comparable to the known span of the existence of mankind as a species since the first manlike creatures appeared on earth probably less than a million years ago

In the case of mutations with dominant or semidominant deleterious effects, equilibria are reached sooner than in the case of recessives Nevertheless a mutant which is lethal when homozygous and which reduces the fitness of heterozygotes by 5 percent would take 20 generations or between 5 and 6 centuries to reach about half of its final equilibrium frequency A mutant which lowers the fitness of homozygotes by 1 percent

and that of heterozygotes by one twentieth of this amount would still be far below the equilibrium frequency in 2 000 generations, or 60,000 years

These calculations may seem to indicate that deleterious mutants never reach their theoretical equilibria in human populations However, it is important to keep in mind that at no time has mankind had a set of normal genes free from deleterious mutations Species—including that of man—do not arise from Adams and Eves, they arise from populations that in one way or another have become separated from the rest of the species Geographical isolation is generally the initial cause of this separation An isthmus sinks under the sea, for example, or in following a retreating glacier some members of a species go to one side of a mountain range, or of a desert, while the rest go to the other side The array of genes present in these separated populations serves as the foundation stock on which still further genetic changes occur Some of man s genetic characteristics may have arisen long ago in our prehuman ancestors Indeed the A B O blood types occur not only in man but in anthropoid apes as well, there is every reason to think that they were present in the common ancestors of men and apes, who lived probably several millions of years ago

The problems of genetic equilibria and the time required for their establishment become very real when we consider the consequences of the genetic damage radiation may do to human populations Suppose for example, that the use of atomic energy for power will become unnecessary within 5 or 10 generations because of advances in the utilization of solar energy The increased mutation rates during these 5 to 10 generations will certainly not suffice to bring every type of deleterious mutation to new and higher equilibrium frequencies We must emphasize, however, that whatever extra mutations will have been induced in mankind will take their toll through the inexorable process of selection This elimination of mutant genes will not happen in a single generation, it will be strung out through a great many future generations This matter will be discussed in more detail in the following chapter

It is important to distinguish between the genetic damage done *per generation* and the *total damage* done to a population Simply because our generation—or our children's generation—may not suffer greatly does not mean that the total damage to mankind will be slight We cannot disregard the damage that will befall future generations even though our emotional involvement in these generations is slight We must remember that no matter how long it may take to re establish a genetic equilibrium the total damage done by a given number of mutant genes is determined by that number and that number alone

7

Genetic Effects of Radiation on Populations

Surveying the Problem

We saw in Chapter 5 that exposure of living beings to high-energy radiations makes mutations more frequent Since most mutations cause some damage to their carriers increased mutation means increased damage In Chapter 6 we considered how mutant genes accumulate in sexually reproducing populations and how natural selection removes mutants from such populations We must now put these things together; we shall try to arrive at a reasoned judgment concerning the probable extent of the genetic radiation damage to living populations, particularly to human populations

It is probable that man made radiations will be a permanent feature of the human environment from now on and that, as a result, mutation rates in man and in other organisms will henceforth be higher than they were in the past On the other hand, it is conceivable that the use of atomic energy will be merely a transient phase in the history of technology and that substitution of solar energy for atomic energy will make wide-

spread use of the latter unnecessary some 5 or 10 generations from now If so mutation rates will increase temporarily but will eventually revert to their present values A temporary in crease in mutation rate could also result from a world war in which atomic weapons were used on a large scale thus exposing a large portion of humanity to abnormally intense radiations We must therefore attempt to deal with two kinds of questions (1) the effect of permanently increased mutation rates on human and other populations and (2) the length of time required to cleanse the gene pools of human populations of the additional mutations produced by a temporary increase in mutation rates

Our problem is complicated by the fact that as we saw in Chapter 6 different kinds of mutations behave differently in populations Completely recessive mutants which harm homozygotes but have no effect at all on heterozygotes accumulate in populations to much greater frequencies than do harmful mu tants that are at least partly dominant and injure heterozygous individuals as well Different again is the behavior of mutants that damage homozygotes but are actually favorable (*heterotic*) in heterozygous condition Mutants with such ambivalent action as we shall see later reach equilibrium levels that are deter mined almost entirely by natural selection and are largely inde pendent of the mutation rate

Then there is the time factor The equilibrium frequencies which were discussed in the last chapter are attained by harmful mutants only after an infinite number of generations during which the mutation rates and selection coefficients must remain constant In reality no biological variable remains constant forever We shall be more realistic if we estimate the magnitude of the genetic load in a population after a limited number of generations For this purpose we can use 10 100 and 1 000 generations as convenient milestones in the history of the population

nera

tion

when in the United States the thirteen original Colo es already established but most of the land west of the Appalachian Mountains was still controlled by the native Indian tribes. *In*

Europe, various absolute monarchs reigned and amused themselves with their favorites and courtiers One hundred generations (2 500 years) ago the Old Testament already governed the lives of a small tribe inhabiting the hills of Judea Although the Pyramids were hoary with age, the classical period had not yet dawned in Greece One thousand generations (25,000 years) ago the human species, *Homo sapiens*, was already in existence, busily shaping stone tools and producing an occasional painter of genius whose cave wall drawings we still admire

Let us try to project these time intervals into the future Events of 10 generations ago are capable of producing strong emotional reactions (witness the requirement for joining the Daughters of the American Revolution), we may be seriously concerned about the state of affairs 10 generations hence. The actions of people 100 generations ago we still evaluate as admirable or reprehensible But we can scarcely hold men of 1,000 generations ago responsible for their deeds, even though these may possibly have affected us Perhaps men living 25,000 years hence will view us as tolerantly—a primitive people not wholly responsible for deeds committed in ignorance, but a people who on occasion produced a masterpiece of thought or action

As far as genetic damage is concerned, mankind is, in the long run, a single population The mutants induced in the survivors of Hiroshima and Nagasaki will not be confined to future populations of these cities Because of the mobility of people, some of these mutants have undoubtedly diffused throughout Japan and, since there will always be some migration from country to country, may find their way to populations of all parts of the world No nation should contemplate with equanimity the possibility of an atomic war, even if that particular nation were sane enough not to participate Nor should anyone feel satisfied provided only he is protected from radiation exposure Although some people, such as radiologists and those who handle radioactive materials, are professionally incurring greater radiation exposures than others, mutations induced in them will enter the common gene pool of the entire population. The only fair measure of the extent of genetic radiation damage

is given by the mean radiation exposure—first of the people of a given country, and then of mankind The future of one man s genes is, ultimately, dependent on that of everyone else's

Radiation-induced Recessive Mutants at Equilibrium

Consider a Mendelian population which, from a certain time on, is exposed to man made high energy radiations Before that time, when the population was exposed only to ' back ground radiations, its genes were mutating "spontaneously at a certain average rate, for which we have used the symbol u (see Chapter 6) The additional increment of mutation, the magnitude of which will of course depend on the amount of additional radiation exposure, may be designated as u' The total mutation rate in the population in question will then be the sum of u and u', this sum we shall write as U.

In homozygous condition, recessive mutant genes are likely to produce hereditary diseases, malformations or constitutional weaknesses Suppose that a mutant lowers the fitness of its car riers by a fraction s As shown in Chapter 6 this mutant will accumulate in the population to an equilibrium frequency value of $q = \sqrt{u/s}$ This equilibrium will be reached when the mutation rate, u, equals the rate of elimination (genetic death) of the mutant genes The elimination rate will, then, be sq^2 (the selection coefficient, s, multiplied by the square of the frequency of the mutant gene in the gene pool, q^2) The increased mutation rate, U, will raise the equilibrium level, this new equilibrium level is easily estimated as $\sqrt{U/s}$ The total rate of genetic death ($U/s \times s$) will now be U instead of u, the in creased genetic damage produced by the increased mutation rate will evidently be $U - u = u'$, the radiation induced increment of mutation

All this may still seem too abstract. To illustrate the magni tude of the genetic damage which exposures to radiation may induce, we shall give an example using numerical values ob-

tained from studies of Drosophila We do not imply that these values are identical with those for man, but they can serve to illustrate the method used in estimating the magnitude of radi ation induced genetic damage which exposures to radiation may produce In man, the genetic damage would, if anything, be greater than in Drosophila

Experiments have shown that in Drosophila not treated with any mutation inducing radiations, about 5 sex cells out of every 1,000 contain a newly arisen recessive lethal mutation in a certain chromosome (the so-called second chromosome) The spontaneous mutation rate for this particular chromosome is, thus 0 005, or 5×10^{-3} The mutation rate in the progeny of flies treated with 1,000 r of x rays is almost ten times as large Hence, about 5 chromosomes per 100 will carry a newly arisen lethal the mutation rate per chromosome will be 0 05, or 5×10^{-2}

From other experiments (see Chapter 5) it has been esti mated that the second chromosome of Drosophila contains, roughly, 500 genes (loci) capable of yielding recessive lethal or other deleterious mutants Drosophila also has another chromosome (the third), which contains about as many genes as the second The two chromosomes together have, then, about 1,000 genes capable of mutation Using these figures, we can estimate the average mutation rate per gene The spontaneous mutation rate per gene is evidently $u = 0\ 005 - 500 = 0\ 000{,}01$, or 1×10^{-5}, the rate after administration of 1,000 r of x rays is $U = 0\ 05 - 500 = 0\ 000\ 1$, or 1×10^{-4} Since the frequency of induced mutations is proportional to the amount of radiation applied, it follows that the increment of mutation per gene per 1 r of radiation (u') is about $0\ 000{,}1 - 1{,}000 = 0\ 000\ 000{,}1$, or 1×10^{-7}.

It is interesting to note that this figure lies in the midrange of several estimates made by Russell and his collaborators for the average mutability of the 7 genes in mice (see Chapter 5, page 86) The values obtained by these workers for "chronic" radiation were 2×10^{-7} and 3×10^{-7} mutations per gene per 1 r for males and females respectively, for "acute" radiation they obtained values of 4×10^{-8} and 5×10^{-8} for females and males

respectively The reader will see that we are not being com pletely "unrealistic" in choosing fruit flies as the starting point of our argument!

Let us now summarize the estimates for *Drosophila* in the following tabulation

Mutation rate, spontaneous, second chromosome	0 005, or 5×10^{-3}
Mutation rate, 1,000 r of radiation, second chromosome	0 050, or 5×10^{-2}
Number of genes second chromosome	500, or 5×10^{2}
Spontaneous mutation rate, u, per gene	0 000,01, or 1×10^{-5}
Induced mutation rate, u', per gene, per 1 r	0 000,000,1, or 1×10^{-7}
Genes in the second and third chromosomes	1,000, or 1×10^{3}

Here we are forced to make a step in our calculations which involves the greatest risk of error For reasons discussed in Chapter 5, most genetic studies have been made with mutations yielding recessive lethal genes But we suspect that lethal mu tants—that is, absolutely fatal hereditary diseases—represent a minority of all mutations Since the over all fraction of a popu lation which is lost through death and incapacitation caused by mutation is equal to the mutation rate and is independent of the degree of harm to afflicted individuals (see Chapter 6), it becomes necessary to estimate what fraction of all mutations is lethal and what fraction produces less pronounced damage Several geneticists have estimated that the lethal fraction is about one fifth, and for want of a more reliable figure we shall use this estimate We shall also ignore the fact that Drosophila has another large chromosome in addition to the second and third, this chromosome is involved in the determination of sex and its behavior in populations is a separate story, which need not concern us here

We have seen that the spontaneous mutation rate produc ing lethals in *Drosophila* is $u \approx 0\ 000\ 01$ per gene per genera tion For 1,000 genes this means that about $0\ 000\ 01 \times 1{,}000 \approx 0\ 01$, or about 1 percent of the sex cells, carry a newly arisen spontaneous lethal in each generation The incidence of *all* mutations is, then, $0\ 01 \times 5 = 0\ 05$, or 5 percent per generation

This means that at equilibrium about 5 percent of the individuals in each generation will be subject to genetic death owing to spontaneous mutation

By how much will the rate of genetic death be increased if a population is irradiated? The Genetics Committee of the National Academy of Sciences has recommended that the mean exposure of individuals in human populations should not be allowed to exceed 10 r before the age of 30 years (the age corresponding to about the middle of the childbearing period in the population of the United States) In Drosophila the lethal mutation rate per gene per single roentgen is as we have seen above 0 000 000 1 This we should multiply by 10 (the number of roentgens to which the population may conceivably be exposed) and also by 1 000 (the number of genes) and by 5 (to take into account the deleterious mutants that are not fully lethal) The result is 0 005 or 0 5 percent In other words at equilibrium the rate of elimination of harmful mutants (the frequency of genetic death) in a population continuously exposed to 10 r of man made radiation would be 5 5 percent instead of 5 0 percent Is this increase large enough to worry about? A 10 percent increase in the frequency of hereditary ills in the suffering of the families involved and in the financial burden imposed not only on those families but on the population as a whole is certainly something to consider seriously

Radiation induced Recessive Mutants on the Way to Equilibrium

The calculations above tell us what happens to a population exposed to radiation for an infinite number of generations or at least for a number large enough to permit all kinds of mutants to approach their equilibrium levels We must also consider the more immediate generation by generation aspect of the problem

Let us assume that a population is from a certain time on exposed to a certain amount of man made radiation in every generation Let us also assume that this population had reached

an equilibrium state for spontaneous mutations before the exposure to radiation began We may, then, limit ourselves to consideration of the effects of radiation induced mutants, which are added to the mutants arising spontaneously Without radiation, a mutant arising spontaneously at a rate u per generation will reach an equilibrium frequency in the gene pool of $q = \sqrt{u/s}$ (see page 112) The additional mutations induced by the radiation arise at a rate u' per generation After 1, 2 3, . n generations of irradiation, there will be $1u'$, $2u'$, $3u'$, nu' induced mutants added to the gene pool If n is small the frequency of the mutant gene in the gene pool in the n^{th} generation will be approximately $q_n = q + nu'$, or $q_n = \sqrt{u/s} + nu'$ The frequency of individuals homozygous for this mutant gene in the population will, consequently, be $q_n^2 = (\sqrt{u/s} + nu')^2 = u/s + 2nu' \sqrt{u/s} + (nu')^2$ Since the quantity $(nu')^2$ will generally be small enough to be neglected, the increase in the proportion of homozygous individuals ascribable to the radiation exposure may be adequately estimated as $q_n^2 - q^2 = 2nu' \sqrt{u/s}$

How great an effect will this increased frequency of mutant homozygotes have on the welfare of the population? How many genetic deaths will it cause? This effect is measured as the product of the radiation induced increment of homozygous mutants times the degree to which these mutants are incapacitated by genetically conditioned ill health—$(2nu' \sqrt{u/s})s = 2nu' \sqrt{us}$

This formula is worth examining in detail, since it discloses some important facts First of all, notice that the formula contains the value s, the selection coefficient This means that the damage done by the additional radiation induced mutants after a specified number of generations but before a new equilibrium has been reached is not independent of the degree of harm they produce The more drastic mutants—lethal or semilethal hereditary diseases—will cause greater harm than will milder disturbances Notice also that the formula contains the value u, the spontaneous mutation rate This means that the more frequently the mutation arises spontaneously, the more harmful the radiation induced increment of mutation will be The reason for this is that most homozygous mutant individuals carrying an induced mutant gene will have a mutant of spontaneous origin

as the other member of their homozygous pair (Homozygous individuals carrying 2 induced mutant genes will have the frequency $(nu')^2$, which we have neglected as insignificant)

Now let us try to translate this algebra into figures whose meaning is easier to visualize Consider recessive mutants which are lethal when homozygous, and which consequently have a selection coefficient $s = 1\ 0$ As before, assume that the organism has 1,000 genes capable of producing such lethal mutants, that the spontaneous mutation rate per gene is $u = 0\ 000{,}01$, and that the induced mutation rate per gene per roentgen of radiation is $u' = 0\ 000{,}000{,}1$ Suppose that, beginning at a certain time, the population is exposed to 10 r of radiation per generation, so that the value u' equals 0 000,001 How many additional genetic deaths (lethal homozygotes) will occur in this population 10, 100 and 1,000 generations after the beginning of irradiation ($n = 10$ 100 and 1,000)? We may now substitute these values in the formula $2\ nu'\ \sqrt{us}$ given above The results are as follows:

10 generations	0 000 06
100 generations	0 000 6
1,000 generations	0 006

The estimate for 1,000 generations is obviously not valid, it seems higher than would be expected when the new equilibrium value (0 001) is reached In making our approximations we have neglected the slow but steady elimination of the newly induced lethals from the population Our formula is not good enough to calculate the effects of additional radiation induced lethals for 1,000 generations of continuous irradiation But the estimates for 10 and for 100 generations are reasonably accurate After 10 generations the frequency of genetic deaths increases by 0 006 percent, after 100 generations by 0 06 percent, at equilibrium it should be increased by 0 1 percent. In other words, after 100 generations of continuous irradiation more than half of the final equilibrium frequency will have been attained Remember, though, that there will be some additional genetic deaths from the very start, one cannot *decrease* the proportion of homozygous individuals by *increasing* the frequency a given type of mutant gene

As stated above, only about one fifth of all mutations act complete lethals About four fifths range from semilethal

only slightly deleterious or nearly neutral conditions Unfortunately, there is no reliable method of estimating how the total genetic damage gradually increases after various numbers of generations of irradiation The difficulty is that we have no estimates, even for Drosophila, of just what arrays of the selection coefficient (s) and of the mutation rates (u and u') we are faced with in attempting to encompass all kinds of mutations that may arise

We shall, accordingly, confine ourselves to consideration of a single example Suppose that an organism has 1,000 different genes (loci), with an average mutation rate per gene per generation four times as large as we have assumed above for lethal mutants (that is, $u = 0\ 000{,}04$ and $u' = 0\ 000\ 000{,}4$ per roentgen of radiation, instead of the 0 000,01 and 0 000,000,1 respectively estimated for lethals) Suppose, further, that the mutations lower the fitness of homozygous individuals by 10 percent (that is the selection coefficient is $s = 0\ 1$) We can now use the formula $2nu' \sqrt{us}$ for the increase of genetic damage The computation gives the following figures

10 generations	0 000,16
100 generations	0 001,60
1,000 generations	0 016,00

The increase in the expected frequency of mutant homozygotes at equilibrium will be about 0 004 We see, then, that about *100* generations of *continuous irradiation must elapse* before a sizable fraction of the increased damage expected at equilibrium is realized Once more our formula proves to be too crude for the 1,000 generation interval, our calculations would indicate a greater amount of harm after 1,000 generations *than at equilibrium This, of course,* cannot be so, the fault lies in neglecting the term $(nu')^2$.

Radiation-induced Mutants That Harm Heterozygotes

Some geneticists question whether mutant heterozygotes are ever completely identical with the "normal" (that is, non

mutant) homozygotes This is perhaps one of the most important unsolved problems of modern population genetics, and it happens to be critical for an estimation of the genetic radiation damage As shown in Chapter 6, if a mutant gene incapacitates heterozygotes even slightly, its equilibrium frequency in the population is much lower than it would be if the mutant were completely recessive Nevertheless the genetic damage produced by incompletely recessive genes is twice as great as that resulting from complete recessives with like mutation rates Conversely, if the heterozygous carriers of a mutant gene are more fit than the noncarriers (a possibility to be discussed in Chapter 8), the fitness of the population as a whole may be augmented even though the homozygous condition results in incapacitation or even death What proportion of the mutants arising in man and in other organisms decreases, increases, or leaves unchanged the fitness of heterozygotes can be determined only by future research Such research is urgently needed

Let us consider first how mutants that injure heterozygous carriers behave in unirradiated and in irradiated populations As before, let u and u' stand for the spontaneous and the induced mutation rates, U for the sum of the two, s for the loss of fitness in mutant homozygotes and hs for the damage in mutant heterozygotes As shown in Chapter 6 the equilibrium frequency of the mutant gene in the gene pool of a nonirradiated population will be approximately $q = u/hs$ for most likely values of h and s, and the genetic damage caused by this gene will be approximately $2u$ Irradiation adds u' mutations in each generation The equilibrium frequency of the mutant gene will, then be U/hs, and the genetic damage $2U$ It is possible that some of the mutations that arise are completely recessive and others incompletely so The total genetic damage to the population caused by spontaneous and induced mutations when all the mutants have reached their equilibrium frequencies will then lie somewhere between U and $2U$ In our present state of ignorance this is as much as we can say about the situation

We must however, ask how rapidly the new genetic equilibria for incompletely recessive injurious mutants will be reached in irradiated populations, and how great the genetic damage is likely to be on a generation by generation basis A

before, suppose that the organism has 1,000 genes (loci) which mutate spontaneously at a rate $u = 0\ 000\ 01$ to a condition which is lethal to homozygotes We have seen above (see page 132) that, if the mutants are completely recessive, the total genetic damage to the population will be $1,000u = 0\ 01$, or 1 percent We have likewise seen that if the mutant also injures heterozygous carriers, the genetic damage produced at equilibrium will be about twice as great, $2 \times 1,000u = 0\ 02$, or 2 per cent This doubling of the amount of damage applies for all practical purposes whether the harm to individual heterozygotes is great or small

Now, without trying to follow the algebra needed to make the calculations, let us consider two numerical examples that will help to visualize the important features of the situation Suppose that the mutant genes which are lethal to homozygotes reduce the fitness of heterozygotes by 5 percent or by 2 percent—that is, that the value h is 0 05 or 0 02 At the time irradiation commences, spontaneous mutation has already reduced the theoretically possible optimal fitness by about 2 percent Assume as on page 133, that the population is exposed to 10 r of radiation per generation, the value which, according to the Genetics Committee of the National Academy of Sciences, should not be exceeded in human populations The increment of radiation induced damage afflicting any one generation, added to the 2 percent (0 02) damage resulting from spontaneous mutation will be as follows

Generations	$h = 0\ 05$	$h = 0\ 02$
5	0 000 46	0 000 20
10	0 000,80	0 000 36
25	0 001,44	0 000 80
50	0 001,82	0 001 28
100	0 001,98	0 001 74
Infinity	0 002 00	0 002 00

What this tabulation shows is that the greater the degree of injury to heterozygous carriers, the more rapidly the equilibrium frequencies for incompletely recessive deleterious mutants

are attained in irradiated populations Accordingly, the genetic damage from such incompletely recessive mutants will be felt sooner if the heterozygotes are appreciably incapacitated than if they are not To visualize the situation even more easily, con sider dominant lethal mutants ($s = 1$, $h = 1$) Since such mu tants kill every individual who carries them, all such lethals are eliminated from the population in the same generation in which they appear, and the equilibrium is accordingly, reached in a single generation By contrast, equilibria for completely reces sive mutants are reached very slowly (see page 135).

Recessive Mutants Produced by Temporary Radiation Exposures

In the foregoing pages we have considered the radiation damage resulting when every generation of a Mendelian popu lation is beginning at a certain time, exposed to a certain amount of mutagenic radiation We have tried to estimate the amount of the genetic damage caused per generation under various specified conditions It is pointless to attempt to sum up the total damage produced through all generations given infinite time and an infinite number of generations the total damage will also be infinite Now we shall face a different prob lem—the damage caused in a population exposed to radiation for a limited time only Here we wish to find out not only how much damage will result in any one generation but also what the total damage caused in successive generations will be This type of problem is particularly important in evaluating the genetic damage that would be produced by such a contingency as a nuclear war We concern ourselves with the summation of damage through successive generations because we believe that a person is morally obliged to consider how his actions will affect other human beings even those whom he will never meet in the flesh.

If a population is exposed to radiation for a small number of generations only, the number of recessive deleterious mutants

introduced into the gene pool is easy to calculate It is very nearly equal to the number of generations during which the radiation is applied, times the frequency with which mutations are induced in each generation (nu') Here we may use once more the figures given on page 132 If a population is exposed for 10 generations to 10 r of man made radiation, there will be induced $10 \times 10 \times 10^{-7}$, or 10^{-5} new recessive lethal mutants per gene Since the population contains some similar (allelic) lethal mutants that have arisen spontaneously, a few radiation induced lethals may be eliminated immediately if they happen to form homozygous individuals However, the fraction of new lethals eliminated within a short span of time will be very small the bulk of them will be lodged in the gene pool of the population when the irradiation is terminated (Remember that 10 r *of radiation applied over a period of 10 generations will* produce the same number of mutants as 100 r applied to a single generation)

How can we measure the total damage caused by the deleterious genes induced by the irradiation? The task happens to be less formidable than it may seem Consider a population in which lethal mutants of each gene locus have reached their equilibrium frequency The recessive lethal mutants of a given gene a, will have, then, a certain frequency, q, and the normal genes, A, will have the frequency p, where $p = 1 - q$ Let us assume that radiation has induced an additional increment i, of the lethal genes a, so that the total frequency of a in the gene pool is $q + i$ (and the frequency of A will make up the remainder—that is, $1 - q - i$) The individuals born in this population will be of three kinds homozygotes for the nonlethal gene A, heterozygotes for the lethal and the nonlethal Aa, and homozygotes for the lethal, aa These last will be eliminated from the population by death

The genes carried in the individuals who are eliminated must be considered further The individuals homozygous for the lethal a are again of three kinds those carrying two old lethals those inheriting an old and a new lethal and those homozygous for two 'new' lethals The composition of the population can, then, be represented by the following diagram

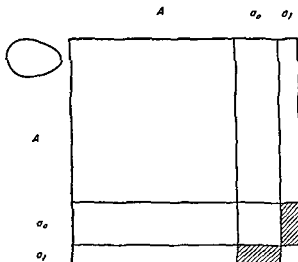


FIGURE 14 The elimination of newly induced recessive mutant genes from a population Before irradiation the population contained normal genes (A) and "old" recessive mutants (a_o) Following a period of radiation the supply of a mutants is increased by the addition of some newly induced ones (a_i) If the effect of these mutants both a_o and a_i, is completely recessive a_i genes will be eliminated only through the reduced viability or reproductive capacity of a_ia_o and a_ia_i individuals Since the frequency of a_o will ordinarily be many times that of a_i after a limited exposure of the population to radiation the really important means of elimination will be by way of a_ia_o individuals (shaded in diagram) a_ia_i individuals will be extremely rare and may be ignored for purposes of calculation This situation is analyzed in detail in the text

(Figure 14) The "old" lethals are those denoted as a_o and the induced or "new" ones as a_i

In general the fraction i will be small compared with q, therefore most of the newly induced lethals eliminated from the population will be those eliminated in association with "old" lethals Elimination of newly induced lethals by way of

$a_i a_i$ individuals is so rare that it can be neglected. However, some a_o lethals will be lost because of the presence of a_i therefore, we will simply replace these old genes out of our stock of new ones We do this by saying that there are $2qi$ new lethals lost in each generation, half of these are actually lost in the lethal homozygotes while the other half are 'lost" because we arbitrarily call qi new lethals 'old' to maintain the proper frequency of the latter

If the frequency of induced lethals per gene locus at the termination of the irradiation is i, their frequency in the next generation is $i - 2qi$ or $i(1 - 2q)$ In the following generation the frequency of $i(1 - 2q)$ is reduced to $[i(1 - 2q)] - 2q[i(1 - 2q)]$ This is equivalent to $i(1 - 2q)(1 - 2q)$, or $i(1 - 2q)^2$ In succeeding generations the frequency of these lethals becomes $i(1 - 2q)^3$, $i(1 - 2q)^4$, $i(1 - 2q)^{n-1}$

In each generation, the frequency of individuals who are eliminated from the population because they are homozygous for the lethal a equals $2q$ times the remaining frequency of the lethal, thus

Generation	1	2	3	n
Lethal frequency	i	$i(1-2q)$	$i(1-2q)^2$	$i(1-2q)^{n-1}$
Individuals lost	$2qi$	$2qi(1-2q)$	$2qi(1-2q)^2$	$2qi(1-2q)^{n-1}$

The total frequency of individuals lost from the population in the course of eliminating the induced lethals is equal to

$$2qi\,[1 + (1 - 2q) + (1 - 2q)^2 + \quad]$$

Since $1 - 2q$ is less than one, the series within the brackets has a finite sum, even though the number of terms is infinite This sum is $1/2q$ Therefore, the sum of the frequencies of eliminated individuals is $2qi \times 1/2q$, or simply i Assuming that the population remains fairly constant in size, the *number* of individuals eliminated in all future generations will be equal to the fraction i times the number of individuals of which the population is composed in a given generation The greater the average number of people in the world, the greater the absolute number of victims of the short term radiation exposure will be their number relative to the total population will, of course,

gradually decrease as the elimination of the induced mutants progresses.

What, however, will be the average rate of genetic death per generation? If we limit ourselves to considering a relatively small number of generations, n, we shall obtain a fairly good estimate by dividing the sum of the first n terms of the series above by n. This sum is $2qi\,[1-(1-2q)^n]/2q$, and the frequency of individuals eliminated per generation is accordingly $i/n\,[1-(1-2q)^n]$, or very nearly $2qi\,(1-qn)$. Since q is generally a small number (we have used the value 0.003 in previous examples), the frequency of elimination remains very close to $2qi$ for many generations.

As before, we shall attempt to convey an idea of what these formulas mean in practice by considering a numerical example. Assume that the average individual in a population is exposed to 10 r of radiation per generation for 10 consecutive generations, whereupon the exposure is stopped (this may occur, for instance, if a safe substitute for atomic energy is eventually discovered). During the 10 generations, 10^{-5} recessive lethal mutants will be induced in every gene capable of such mutation (see page 140). These induced lethals will eventually be eliminated by the death of their homozygous carriers. Assuming that the world population of the human species is stabilized at 3 billion persons (3×10^9), this would mean 30,000 genetic deaths caused by mutants at each gene locus, or 30 million deaths for 1,000 genes.

Lest 30 million deaths seem fantastic, remember that they will occur over a time interval infinitely long—literally time without end. More to the point is how many genetic deaths will be taking place per generation within some foreseeable future, say 20 generations. To arrive at this number we may use the formula $2qi(1-qn)$ given above. If the spontaneous mutation rate is close to 0.000 010, the value q will be roughly 0.003 (the square root of 0.000 010). With $i = 10^{-5}$ and $n = 20$, the result *is close to 0.000,000 06. For 1,000* genes *this becomes 0.000 06.* Assuming again that mankind is stabilized at some 3 billion persons this would mean some 180,000 genetic deaths per generation, or about 6,000 deaths annually for the 600 or so years

following the cessation of exposure And this would leave about 90 percent of the induced mutants still to be eliminated!

Nor is this all. We have seen above, in discussing the effects of continuous radiation exposure, that mutants which are dele terious but not lethal to homozygotes are about four times more frequent than the completely lethal mutants, and that they cause, in the aggregate, a greater number of genetic deaths because they, too, will have to be eliminated eventually For deleterious nonlethal mutants, the total number of eliminations, over in finite time, is, analogously with the formula on page 142, equal to

$$2sqi\,[1 + (1 - 2sq) + (1 - 2sq)^2 \quad], \text{ or simply } i$$

For a small number of generations, the average frequency of genetic deaths per generation will be approximately $2sqi(1 - nsq)$, where s is, as usual, the selection coefficient and n is the number of generations A complication arises because, as pointed out above, we do not know the distribution of the values of s nor the rate of mutation for different mutants Other things being equal, the smaller the value of s (that is, the more nearly normal the individuals who are homozygous for the mutation), the smaller the average effect this gene has on the fitness of the population in any one generation Unfortunately, the mutation rate of these genes is higher than that of lethals We may assume, for example, that there are 1 000 genes, each of which mutates to deleterious alleles for which s equals 0 10 at a rate of 0 000 01 per locus Using these assumptions, it is possible to calculate the average effect of these mutations on the population over a period of 20 generations following the cessation of radiation In this case q, the original equilibrium frequency, equals $\sqrt{u/s}$, or 0 02 The frequency, i, of mutations induced during 10 gen erations of exposure to 10 r per generation would be 4×10^{-5} Consequently, the average effect of these mutations on the population over 20 generations would be

$$2 \times 0\ 10 \times 0\ 02 \times 4 \times 10^{-5} \times [1 - (20 \times 0\ 10 \times 0\ 02)],$$

or 0 000,000,15 For 1,000 genes this amounts to 0 000,15

In a world population of three billion persons there would be 3 000,000 000 × 0 000,15 = 450,000 persons eliminated in every generation because they are homozygous for these subvital

recessive defects induced by radiation The value 0 10 which we have assumed for *s* means that the 450 000 persons eliminated account for only 10 percent of all persons threatened with in capacitation there would be 4 500 000 of the latter in each generation *Using 30 years as the length of a generation we* can see that each year some 150 000 persons in the world would be carriers of newly induced deleterious mutations permitting them to survive or reproduce only 90 percent as well as their normal fellow men hence in effect 15 000 persons would be eliminated annually because of these mutant genes

Semidominant Mutants Produced by Temporary Radiation Exposures

As stated above there is a school of thought in biology which denies the existence of completely recessive genes It believes instead that most mutant genes are really semidominant the effects of a mutant being generally similar in homozygotes and heterozygotes although much stronger in the former than in the latter *According to this view every mutant which causes* a hereditary disease when homozygous must produce some frail health *in* heterozygotes Future work may support refute or qualify this extreme point of view nevertheless we should con sider its bearing on the problem of the genetic radiation damage to populations

The task is to estimate the consequences of the temporary exposure of a population to mutagenic radiations We shall proceed in a manner very similar to that employed above for com pletely recessive mutants The diagram in Figure 15 is analogous to that in Figure 14 and contains identical symbols (A repre senting the normal and a the mutant gene alleles a_0 and a_i the mutants produced spontaneously and those induced by radi ation) The shaded part of the diagram indicates the hetero-zygotes which carry one normal (A) and one radiation induced mutant (a) gene If such heterozygotes are less fit than

Attempts to Detect Genetic Radiation Damage in Man

The foregoing pages of the present chapter may have struck the reader as too theoretical We have operated with formulas that may be valid enough in theory, but in attempting to illustrate their meaning by examples we were forced to use numerical values derived largely from genetic experiments on Drosophila Even then we had to confess that these values are at best rough approximations In a way, this situation is not quite so bad as it may seem The basic genetic processes operating in Mendelian populations obey the same rules in all biological species reproducing sexually and avoiding marriage of close relatives If a deleterious recessive mutant arises at a rate u per generation, its equilibrium frequency will be $\sqrt{u/s}$ in large populations of flies mice, men, or elephants But we have no right to assume without sufficient evidence that the values of U and s and the incidence of recessive, semidominant, and heterotic mutants are the same in Drosophila as in man To understand the genetics of human populations, research on Drosophila and on man is equally important and indispensable for the results of such research are complementary and mutually enlightening

Attempts have been made to detect genetic radiation damage in human populations By far the most extensive, careful, and costly work of this sort has been carried out under the leadership of J V Neel and W J Schull on the survivors of the atomic blast at Hiroshima and Nagasaki In all, the newborn children of some 20,000 women and 14 000 men who were sufficiently close to the blasts to receive anywhere from 8 to 200 r of radiation were examined Among 33 181 parturitions in which at least one parent was irradiated, there were 516 stillborn infants The investigators also studied a control sample—31,559 parturitions in which neither parent was known to have suffered irradiation In this control sample there were 408 stillbirths The frequency of stillbirths in families of irradiated par

ents was, accordingly, 1 64 percent, which is ostensibly higher than the frequency 1 29 percent in the control sample

It is tempting to ascribe this increase in the frequency of stillbirths to radiation induced dominant or semidominant deleterious mutants Other explanations are not, however, entirely ruled out not all stillbirths are caused by genes, and the small excess of their frequency among the infants of irradiated parents may be due largely to statistical errors of sampling or other, undetected causes Neel and Schull also record 300 infants born with congenital malformations of various kinds among 33 527 live births to parents of whom at least one was irradiated The corresponding figure for the control series is 294 infants with malformations among 31,904 births There is no indication that malformations are more frequent in the irradiated series

S H Macht and P S Lawrence, and also J F Crow, have utilized another source of data They sent questionnaires to about 6 000 American radiologists and also to those physicians who are not constantly working with x rays or other radiations during the performance of their professional duties The radiologists are undoubtedly exposed to many small doses of radiation, although it is not possible to determine just how many roentgens they accumulate during their lifetime A total of 766 abortions and stillbirths and 328 congenital malformations among infants born alive, were recorded among 5 461 births in families in which the father was a radiologist In the control series there were 548 abortions and stillbirths and 216 malformed infants among 4 484 births Critical examination of these results shows that there is an ostensible but statistically not significant, increase in the incidence of abortions and stillbirths, but an apparently significant increase in congenital malformations in the offspring of radiologists

What conclusions can be drawn from these data? They would surely be inadequate to prove that radiation produces mutations if we did not possess overwhelming evidence of this from experiments on organisms other than man But it is nothing short of ridiculous to argue, as some people have attempted to do, that radiation may not be mutagenic in man Even with

the impressively large number of observations reported by Neel and Schull from Japan, one would not expect enough induced dominant and semidominant lethals and semilethals to yield striking differences in the number of stillbirths and malformations between the irradiated and the control series. We need qualitative and quantitative data concerning spontaneous and radiation induced mutations in man But it would be a waste of time, effort, and money to undertake research on man merely to prove that he, just as every other living organism studied, is subject to the mutagenic action of radiation.

8

Some Unsolved Problems

Introductory Remarks

A scientist knows certain things to be true or at least overwhelmingly probable, it is his duty to affirm these things even in the face of opposition from those who, owing to ignorance or to some emotional bias wish to deny them Such is, for example, the fact that the living world, including man, is a product of evolutionary development We have to maintain that this is so, even though the laws of certain states still prohibit such an affirmation Similarly, we have to assert that high energy radiations can produce genetic damage in human populations On the other hand, a scientist must in all humility, admit that he does not know the answers to many riddles of nature there is no reason for him to hide his ignorance Nevertheless, when he tries to do his part in educating the public, the temptation arises to oversimplify his story by the omission of difficulties and uncertainties Up to a point, such omissions are justified But there is always a point beyond which simplification borders on falsification

In the foregoing chapters we have pointed out time and again that the presently available understanding of population genetics is imperfect and that its inadequacy makes some of

our conclusions concerning the genetic damage produced by radiation highly tentative In the following pages we shall discuss some topics which in our opinion are particularly in need of clarification This should enable the reader to judge for himself the weakest links in the geneticist s conception of what a misuse of radiation may portend for the future of mankind We also hope to call the attention of our colleagues biologists and geneticists to the need for research on these unsolved problems for we believe that the research effort now being exerted in studies of radiation biology and radiation genetics must include an appreciation of their importance

Heterosis and Mutation

In Chapters 6 and 7 we discussed two kinds of deleterious mutant genes and their effects on the fitness of populations The simplest situation obtains when a mutant harms homozygotes but has no effect at all on heterozygous carriers The other kind of mutants discussed damage heterozygotes as well as homozygotes though the latter more severely than the former We saw that regardless of the severity of the damage produced in afflicted individuals (ranging from complete lethality to only a mild impairment of health) the total damage to the population is approximately the same It may be equal to the mutation rate or to double the mutation rate or it may lie between these values We must now consider an even more complex but very interesting situation of ambivalent mutants—those which impair fitness when homozygous but improve that of their heterozygous carriers

That such mutants do occur is suggested on a gigantic scale by hybrid corn For the past quarter of a century the bulk of all corn planted in the United States and more recently elsewhere has consisted of hybrids between pairs of different lines These heterozygotes are superior in yield to the best open pollinated field varieties of corn which were planted before the invention of hybrid corn and its introduction into general use

To see how this hybrid vigor, or *heterosis* (these terms are synonymous), operates within populations we may consider a numerical example before turning to generalization

The genes we are to consider lack the dominance and recessiveness, so we shall designate one form of the gene as a_1 and its mutant form (allele) as a_2 The vigorous heterozygotes, a_1a_2 enjoy the higher fitness, while the homozygotes a_1a_1 and a_2a_2 are, respectively, 80 percent and 20 percent as fit as the heterozygotes What will happen in a population in which both a_1 and a_2 are represented? We shall state without proof that the frequencies p of a_1 and q of a_2 will be respectively 0 8 and 0 2 in the gene pool of the population Let us then, make a ledger sheet of the fitness of this population It appears as follows

Genotype	*Frequency*	*Fitness*	*Frequency* × *Fitness*
a_1a_1	$p^2 = 0\ 64$	0 8	0 512
a_1a_2	$2pq = 0\ 32$	1 0	0 320
a_2a_2	$q^2 = 0\ 04$	0 2	0 008
Average fitness of the entire population			0 840

The most important fact disclosed by this table is that the over all fitness of the population (obtained by summing the products of the fitness of each genotype times its frequency in the population) has the value 0 840 Yet a population containing only the better allele, a_1, would have a fitness of only 0 80 (frequency 1 00 times fitness 0 8) In other words, the introduction into the population of the mutant allele a_2 has *improved* the over all fitness of the population despite the fact that this mutant allele is deleterious and adds to the genetic load of the population by producing a weak, poorly adapted homozygote, a_2a_2 with a fitness of only 0 2 This amounts to saying that a gene which produces a hereditary disease when homozygous may still benefit the population as a whole provided that it is advantageous in heterozygous individuals

Of course, one may rightly say that an even better population would be one consisting entirely of the heterotic heterozygotes, a_1a_2 True enough, and this is precisely what happens

when hybrid corn seeds giving only heterozygous plants are sown The trouble is, however, that a population consisting of vigorous heterozygotes cannot maintain itself by sexual reproduction According to the Hardy Weinberg Theorem, a_1a_2 individuals would in the very next generation give a progeny consisting of only 50 percent a_1a_2, 25 percent a_1a_1, and 25 percent of the ill adapted a_2a_2 The fitness of such a population would be only 0 75 This is why a farmer must buy his hybrid corn seed for every planting instead of saving his own seed from the previous harvest

The situation can be generalized as follows Assume that the fitness of the heterozygote a_1a_2, is 1 00 while the fitnesses of the two homozygotes is $(1 - s)$ for a_1a_1 and $(1 - t)$ for a_2a_2 Although we cannot give the proof in this book it can be shown that the relative frequencies of the genes a_1 and a_2 establish a stable equilibrium the equilibrium frequency of a_1 being $t/(s + t)$ and that of a_2 being $s/(s + t)$ The letters s and t stand for the selections coefficients discriminating against the homozygotes The ledger sheet of the fitness of the population is as follows

Genotype	*Frequency*	*Fitness*	*Frequency × Fitness*
a_1a_1	$p^2 = t^2/(s + t)^2$	$1 - s$	$t^2(1 - s)/(s + t)^2$
a_1a_2	$2pq = 2st/(s + t)^2$	1	$2st/(s + t)^2$
a_2a_2	$q^2 = s^2/(s + t)^2$	$1 - t$	$s^2(1 - t)/(s + t)^2$
Average fitness of the entire population			$1 - [st/(s + t)]$

If the algebra seems terrifying take note only of the fact that the fitness of the population in which both a_1 and a_2 occur is $1 - st/(s + t)$ and that this value is larger than both $(1 - s)$ and $(1 - t)$ which measure the fitness of a population consisting of a_1a_1 or a_2a_2 homozygotes only This is true even if the allele a_2 produces, when homozygous, a lethal hereditary disease—that is if $t = 1$ The population has the highest fitness only if it contains some a_1a_2 heterozygotes Furthermore, the fitness of the population is highest at the equilibrium frequencies of the two alleles any deviation from these frequencies (caused for

example, by an attempt to cull out the less desirable of the two) results in a decrease in the mean fitness of the entire population

Suppose that both homozygotes a_1a_1 and a_2a_2 are handicapped equally compared to the vigorous heterozygote This means that the coefficients s and t are equal $s = t$ Both genes will therefore, have equal frequencies in the gene pool 0 5 The gene a_1 will have the frequency $t/2t = 0\ 5$ and a_2 the frequency $s/2s = 0\ 5$ Now suppose that s is much larger than t, so that a_1a_1 is nearly as good as the heterotic a_1a_2 while a_2a_2 is very inferior or even lethal Natural selection will make the population mostly homozygous for a_1a_1 However—and this is important—the gene a_2 will be retained in the population by natural selection It will be carried chiefly in heterozygotes a_1a_2 but some infirm homozygotes a_2a_2, will though rarely, be born

We have already pointed out above that it is not well known how often mutations arise which possess properties like those of a_2 in the example just given Some geneticists believe that such heterotic mutants are rare and hence unimportant in our evaluation of genetic radiation damage Other geneticists take seriously the possibility that such mutants may be important Statements in newspapers and magazines have referred to disagreements among geneticists concerning the dangers of genetic damage produced by radiation exposure These statements are misleading The real differences of opinion concern this problem of superior fitness produced by heterozygosity There is no disagreement about radiation exposure inducing mutations in human populations Nor does any geneticist doubt that mutations are generally harmful at least in homozygous condition

One of the authors has obtained recent experimental evidence that heterotic mutants may be far more common at least in Drosophila than had been suspected previously The essence of these experiments is as follows It had been known previously (see Chapter 6 page 117) that natural populations of Drosophila carry enormous loads of genetic variants which are more or less deleterious if permitted to become homozygous As stated on page 117, virtually all chromosomes in Drosophila populations

act as lethal, semilethal, or subvital mutants when carried in double dose in the same individual (that is, if inherited by an individual both from the mother and from the father) Several strains of flies homozygous for such subvital chromosomes were chosen By means of a method which we cannot describe here in detail, the viability of these homozygotes were compared with that of flies which were genetically similar, except that they had one of the two chromosomes of the pair treated with a small (for Drosophila) dose of x rays (500 r) The viability of the flies carrying an irradiated chromosome appeared slightly but significantly *higher* than that of the nonirradiated controls

Should these experimental findings be confirmed, it would follow that mutations tend frequently to produce hybrid vigor in heterozygous condition This might require a revision of the assumption that mutation is almost always harmful not only to *homozygotes (which remains true) but also to heterozygotes* (which is now in doubt) Some inflow of new mutations may well be necessary to maintain a variety of genes in the gene pool of a Mendelian population Indeed, except for mutation, all known processes that operate in natural populations tend to produce genetic uniformity and homozygosis The process of mutation is, then, two-faced as far as the fitness of the population is concerned Mutant homozygotes may suffer, but the genes responsible may be retained in the population because their heterozygous carriers are, in fact, the really "normal" individuals

Genetic Structure of Natural Populations: Classical Hypothesis

This possibility brings us face to face with a very basic question *What is a "normal" man? What*, indeed, is a "normal" Drosophila, or a "normal" representative of any biological species? In everyday social intercourse with people we consider as normal those persons who are free of gross bodily defect and who act in accordance with standards of behavior regarded as acceptable in our society A normal cat or mouse, or Drosophila or corn plant is one which, in appearance and in behavior, does

not differ greatly from other cats, or mice, or Drosophila, or corn plants which we have seen before It must also be able to live *in the environments in which other normal representatives* of its species live, and it must successfully reproduce its kind

And yet there is some diversity among normal people Neither are all normal cats exactly alike, nor all normal Drosophilae How much individuality is compatible with 'normal ity, and what is the source of the differences we observe among individuals? More than 2000 years ago Plato tried to answer these questions He thought that individual humans were all more or less imperfect imitations of an ideal Man, just as individual horses or trees were more or less garbled copies of an ideal Horse or an ideal Tree The ideal prototypes, according to Plato, were eternal and unchanging spiritual entities of ineffable perfection and beauty, their earthly replicas were all defective, but their *shortcomings might be diminished in striving to approach the* Ideal

Although no modern geneticist takes seriously Plato's in genious conception of the relation between heavenly perfection and terrestrial failing, the Platonic mode of thought is deeply ingrained in Western culture and perhaps in ' normal human nature everywhere In some branches of biological research it has not inconsiderable advantages The poet Goethe devised an ideal ' protoplant, which was helpful in understanding the in finitely diverse forms of living plants, and others have used ideal structural plans, schemes, and prototypes to understand and describe the external and anatomic organization of diverse animals The great work of several generations of zoologists and botanists in building a rational classification of all living crea tures was doubtless assisted by the concept of an ideal plan of organization of living bodies

The same line of thought can be used to construct a model of the genetic structure of living populations This model is referred to as the *classical hypothesis* According to the classical hypothesis there emerged, in the evolutionary process, a constellation of genes—a genotype—which makes its carriers live successfully in a certain environment. Thus, the genotype of the human species makes us fit to live in the human environment, the cat s genotype makes cats adapted to the feline environment;

Glossary

ALLELE A variant form of a gene

CELL LETHAL A genetic change that is capable of killing an individual cell possessing it even if this cell is surrounded by others not carrying this change

CENTROMERE A specialized region of a chromosome which is instrumental in the movement of the chromosome during cell division

CHROMOSOME A small body found within a cell nucleus which contains many genes As a general rule one can say that every species possesses a characteristic number of chromo somes

DEOXYRIBONUCLEIC ACID A complex substance composed of fibrous molecules containing phosphoric acid sugar pu rines and pyrimadines it is believed to be the genetic material that controls the composition and structure of protein molecules

DNA *See* Deoxyribonucleic acid

DOMINANT MUTANT An altered form of a gene the effects of which are expressed in heterozygous individuals Partial dominance is used to describe genes whose effect in hetero-zygous condition is not identical with that in homozygous condition complete dominance means that the homo-zygotes and heterozygotes are indistinguishable

DOUBLING DOSE The dose of radiation required to induce the same amount of gene mutation as that which arises spontaneously without radiation

GAMETES Specialized cells that are capable of giving rise to new individuals Sperm are male gametes, eggs, female gametes

GENE LOCUS A region of the chromosome where genes are found which have characteristic effects on their carriers Thus, at one spot on one chromosome in the fruit fly, one detects gene changes that lead to white, apricot, cherry, and eosin colored eyes, one infers that at this spot there is a gene governing eye color and that this gene can change in various ways and produce alleles which give the colors mentioned

GENE MUTATION The transformation of a gene from one form (allele) to another Spontaneous mutations are those which *occur for unknown reasons, induced mutations* are those brought about by certain physical or chemical agents

GENETIC EQUILIBRIUM Stability of the frequencies of various genes in a population, established by opposing tendencies such as formation by mutation and elimination by selection

GENETIC VARIABILITY A property of populations dependent upon the existence of a variety of different forms of many genes It leads to hereditary differences between individuals

GENOTYPE The sum total of all hereditary factors carried by an individual An individual s genotype is determined at fertilization in turn, it limits the variety of gametes an individual can produce

HETEROSIS The possession by heterozygous individuals of certain characteristics (especially in relation to growth or vitality) in excess of the two corresponding homozygotes

HETEROZYGOTE An individual carrying two different alleles at a given gene locus, hence, an individual capable of pro-

ducing two kinds of gametes containing different alleles of that gene

HOMOZYGOTE An individual carrying two identical alleles at a given locus hence an individual capable of producing but one type of gamete as far as that gene is concerned

LETHAL A genetic change that can produce death of an individual Recessive lethals are gene mutations two of which result in death dominant lethals are genetic changes that result in death even though they may be present only in single dose

PHENOTYPE The observable characteristics of an individual determined by his genotype and by the succession of environments in which he developed

RADIOACTIVE SUBSTANCES Substances that emit mutagenic radiations spontaneously

RECESSIVE MUTATION An altered form of a gene whose action can be masked in heterozygous individuals This can be qualified as in incompletely recessive if the effects of the mutant allele are not completely masked in heterozygous condition

ROENTGEN (R) The unit of measurement of x rays and other radiation One roentgen is defined as the amount of radiation which produces $2\,082 \times 10^9$ ion pairs per cubic centimeter of air.

Suggestions for Further Reading

It may well be that some readers of this book will wish to have more information than is found therein regarding some aspects of the problems with which it deals We are giving below a few references to sources that may be used for this purpose

Fundamentals of genetics may be found in any of the numerous available textbooks, such as

ALTENBURG E, *Genetics,* Rev ed New York Henry Holt and Co, 1957

SINNOTT, E B, L C DUNN, and TH DOBZHANSKY, *Principles of Genetics,* 5th ed New York McGraw Hill Book Co, 1958

SRB, A M and R D OWEN, *General Genetics* San Francisco W H Freeman and Co, 1955

STERN, C, *Principles of Human Genetics* San Francisco W H Freeman and Co, 1949

For more information concerning the physical nature of radiations and of atomic energy, see the short but informative book by

HECHT, SELIG, *Explaining the Atom* New York Viking Press, 1954.

Discussions of the mutational loads in human populations, and of the effects of radiation exposures on these loads, have been prepared by committees of several public bodies, such as

Report of the United Nations Scientific Committee on the Effects of Atomic Radiation New York The United Nations

The Biological Effects of Atomic Radiation, Summary Reports Washington, D C National Academy of Science, National Research Council

The Hazards to Man of Nuclear and Allied Radiations London H M Stationery Office

The Effect of Radiation on Human Heredity World Health Organization (Available through Columbia University Press, International Documents Service, New York)

The Effects of Atomic Weapons Washington, D C Superintendent of Documents, U S Government Printing Office

For a most thorough discussion of the genetic consequences of the accumulation of deleterious mutations in human populations, see

MULLER, H J, 'Our Load of Mutations ' *American Journal of Human Genetics, Vol 2 pages 111 176 (1950)*

Contrasting opinions concerning the wisdom of continued production and testing of nuclear weapons have been ably presented and argued by the following

LAPP, R E and J SCHUBERT, *Radiation What It Is and How It Affects You* New York Viking Press 1957

PAULING, LINUS, *No More War!* New York Dodd Mead and Co, 1958

TELLER, E and A L LATTER, *Our Nuclear Future Facts, Dangers, and Opportunities* New York Criterion Books, 1958

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